CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005
21-968 / S-002; 003; 004; 005; 006

Trade Name: Sutent

Generic Name: Sunitinib Malate

Sponsor: C.P. Pharmaceuticals International C.V.

Approval Date: February 2, 2007

Indications: 21-938/S-002; 21-968/S-002: Postmarketing Commitment. #7; provide for revisions to the labeling based on data from the study titled, "A Phase 1 Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors."

21-938/S-003; 21-968/S-003, 004: Postmarketing Commitment. #1,3; provide for revisions to the labeling based on data from the first interim efficacy and safety analysis for 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". The supplements also provide the datasets containing the core imaging facility assessments used to derive the updated response rate for the study titled, "A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma."

21-938/S-004; 21-968/S-005: Postmarketing Commitment #2, 4; provide for revisions to the labeling based on data from the final study report for 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". The supplements also provide follow-up left ventricular ejection fraction (LVEF) data for selected patients on the study titled, "A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma."

21-938/S-005; 21-968/S-006: Postmarketing Commitment #8; provide for revisions to the labeling based on data from the final study report for the study titled, "A Phase I Study to Evaluate the pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function."

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-938/S-002/S-003/S-004/S-005
NDA 21-968/S-002/S-003/S-004/S-005/S-006

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Laurie M. Strawn, Ph.D.
Director, Worldwide Regulatory Strategy

Dear Dr. Strawn:

Please refer to your supplemental new drug applications dated March 30, March 31, August 1, and August 9, 2006, received March 31, April 3, August 2, and August 11, 2006, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SUTENT® (sunitinib malate) Capsules, 12.5 mg, 25 mg, and 50 mg sunitinib equivalent.

We acknowledge receipt of your submissions dated May 23, August 1 and 16 (2), September 26 and 29 (2), October 2 (5), 10, and 13, November 17 (2), 21, and 28, December 5 and 12, 2006, and February 1, 2007.

NDA 21-938/S-002 and NDA 21-968/S-002 were submitted in response to postmarketing commitment #7 from the January 26, 2006, approval letter, and provide for revisions to the labeling based on data from the study titled, *"A Phase 1 Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors"*.

NDA 21-938/S-003 and NDA 21-968/S-003 and S-004 were submitted in response to postmarketing commitments #1 and #3 from the January 26, 2006, approval letter and provide for revisions to the labeling based on data from the first interim efficacy and safety analysis for 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"*. The supplements also provide the datasets containing the core imaging facility assessments used to derive the updated response rate for the study titled, *"A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma"*.

NDA 21-938/S-004 and NDA 21-968/S-005 were submitted in response to postmarketing commitments #2 and #4 from the January 26, 2006, approval letter and provide for revisions to the labeling based on data from the final study report for 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"*. The supplements also provide follow-up left ventricular ejection fraction (LVEF) data for selected patients on the study titled, *"A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma"*.

NDA 21-938/S-005 and NDA 21-968/S-006 were submitted in response to postmarketing commitment #8 from the January 26, 2006, approval letter and provide for revisions to the labeling based on data from the final study report for the study titled, *"A Phase I Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function"*.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions **"FPL for approved supplements NDA 21-938/S-002/S-003/S-004/S-005 and NDA 21-968/S-002/S-003/S-004/S-005/S-006."** Approval of these submissions by FDA is not required before the labeling is used.

We approved NDA 21-968 under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of NDA 21-968/S-005 fulfills the following commitments made under 21 CFR 314.510.

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.

Protocol Submission:	submitted 06/2004
Study Start:	08/2004
Final Report Submission:	by 03/2006

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.

Protocol Submission:	submitted 06/2004
Study Start:	08/2004
Final Report Submission:	by 07/2006

3. Submit raw and derived datasets containing the core imaging facility assessments used to derive the updated response rate and median duration of response on study titled "A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma".

Protocol Submission:	submitted 11/2003
Study Start:	02/2004
Final Report Submission:	by 03/2006

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.

Protocol Submission:	submitted 11/2003
Study Start:	02/2004
Final Report Submission:	by 05/2006

In addition, we have concluded that the following postmarketing commitments from the January 26, 2006, approval letter have also been fulfilled:

7. Submit the completed report and datasets for study titled "A Phase 1 Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors".

Protocol Submission:	submitted 07/2004
Study Start:	08/2004
Final Report Submission:	by 03/2006

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".

Protocol Submission:	submitted 08/2005
Study Start:	09/2005
Final Report Submission:	by 05/2006

Finally, we have reviewed your submission dated September 26, 2006, and conclude that the following commitment from the January 26, 2006, approval letter was fulfilled.

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".**

Protocol Submission:	submitted 06/2004
Study Start:	08/2004
Final Report Submission:	by 07/2006

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitment in your electronic mail submission dated February 1, 2007, listed below.

1. Provide the complete study report and datasets with the final definitive statistical analysis of overall survival and duration of response for the study titled, "A Phase 3, Randomized Study of SU011248 versus Interferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

Protocol Submission:	submitted 6/2004
Study Start:	8/2004
Final Report Submission:	2/2009

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 21-938. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to NDA 21-938. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."**

We also remind you of your outstanding postmarketing study commitments from the January 26, 2006, approval letter. These commitments are listed below. Note that postmarketing study commitment #5 is no longer considered required under the regulations at 21 CFR 314 Subpart H.

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.

Initial Protocol Submission:	submitted 11/2005
Revised Protocol Submission:	by 05/2006
Study Start:	by 03/2006
Final Report Submission:	by 06/2011

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".

Protocol Submission:	submitted 11/2003
Study Start:	12/2003
Final Report Submission:	by 12/2006*

* Note that this postmarketing study commitment is considered 'delayed' according to 21 CFR 314.81(b)(2)(vii)(8). However, we acknowledge your current projected completion date of 12/2007 for this commitment.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to NDA 21-938 and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
2/2/2007 07:25:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUTENT safely and effectively. See full prescribing information for SUTENT.

SUTENT® (sunitinib malate) capsules, oral
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Indications and Usage, Advanced Renal Cell Carcinoma (1.2)	2/2007
Warnings and Precautions, Left Ventricular Dysfunction (5.2)	2/2007
Warnings and Precautions, QT Interval Prolongation and Torsade de Pointes (5.3)	2/2007
Warnings and Precautions, Hypertension (5.4)	2/2007
Warnings and Precautions, Hemorrhagic Events (5.5)	2/2007
Warnings and Precautions, Hypothyroidism (5.6)	2/2007

----------INDICATIONS AND USAGE----------

SUTENT is a kinase inhibitor indicated for the treatment of:

- Gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. (1.1)
- Advanced renal cell carcinoma. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off. (2.1)
- Dose adjustments of 12.5 mg recommended based on individual safety and tolerability. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 12.5 mg, 25 mg, 50 mg (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.1)
- Left ventricular ejection fraction declines to below the lower limit of normal have occurred. Monitor patients for signs and symptoms of congestive heart failure. (5.2)
- Prolonged QT intervals and Torsade de Pointes have been observed. Use with caution in patients at higher risk for developing QT interval prolongation. When using SUTENT, monitoring with on-treatment electrocardiograms and electrolytes should be considered. (5.3)
- Hypertension may occur. Monitor blood pressure and treat as needed. (5.4)
- Hemorrhagic events including tumor-related hemorrhage have occurred. Perform serial complete blood counts and physical examinations. (5.5)
- Hypothyroidism may occur. Patients with signs and symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice. (5.6)
- Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma or severe infection. (5.7)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥20%) are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia, and bleeding. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- CYP3A4 Inhibitors: Consider dose reduction of SUTENT when administered with strong CYP3A4 inhibitors. (7.1)
- CYP3A4 Inducers: Consider dose increase of SUTENT when administered with CYP3A4 inducers. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Gastrointestinal Stromal Tumor

SUTENT is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

1.2 Advanced Renal Cell Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of SUTENT for gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC) is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

2.2 Dose Modification

Dose increase or reduction of 12.5 mg increments is recommended based on individual safety and tolerability.

Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

12.5 mg capsules

Hard gelatin capsule with orange cap and orange body, printed with white **ink "Pfizer" on the cap and "STN 12.5 mg" on the body.**

25 mg capsules

Hard gelatin capsule with caramel cap and orange body, printed with white **ink "Pfizer" on the cap and "STN 25 mg" on the body.**

50 mg capsules

Hard gelatin capsule with caramel top and caramel body, printed with white **ink "Pfizer" on the cap and "STN 50 mg" on the body.**

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pregnancy

Pregnancy Category D

As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of SUTENT in pregnant women. 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 SUTENT.

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

5.2 Left Ventricular Dysfunction

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

More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α). In GIST Study A, 22/209 patients (11%) on SUTENT and 3/102 patients (3%) on placebo had treatment-emergent LVEF values below the lower limit of normal (LLN). Nine of 22 GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction: one patient; addition of antihypertensive or diuretic medications: four patients). Six patients went off study without documented recovery. Additionally, three patients 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. In GIST Study A, 1 patient on SUTENT and 1 patient on placebo died of diagnosed heart failure; 2 patients on SUTENT and 2 patients on placebo died of treatment-emergent cardiac arrest.

In the treatment-naïve MRCC study, 78/375 (21%) and 44/360 (12%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Thirteen patients on SUTENT (4%) and four on IFN-α (1%) experienced declines in LVEF of >20% from baseline and to below 50%. Left ventricular dysfunction was reported in three patients (1%) and CHF in one patient (<1%) who received SUTENT.

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 CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether 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 SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

5.3 QT Interval Prolongation and Torsade de Pointes

SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration (2.2)]*.

5.4 Hypertension

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

Of patients receiving SUTENT for treatment-naïve MRCC, 111/375 patients (30%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 36/375 treatment-naïve MRCC patients (10%) on SUTENT compared to 1/360 patient (<1%) on IFN-α. While all-grade hypertension was similar in GIST patients on SUTENT compared to placebo, Grade 3 hypertension was reported in 9/202 GIST patients on SUTENT (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 18/375 patients (5%) on the treatment-naive MRCC study. Two treatment-naïve MRCC patients, including one with malignant hypertension, and no GIST patients discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 8/202 GIST patients on SUTENT (4%), 1/102 GIST patients on placebo (1%), and in 20/375 treatment-naïve MRCC patients (5%) on SUTENT and 2/360 patients (1%) on IFN-α.

5.5 Hemorrhagic Events

In patients receiving SUTENT for treatment-naïve MRCC, 112/375 patients (30%) had bleeding events compared with 27/360 patients (8%) receiving IFN-α. Bleeding events occurred in 37/202 patients (18%) receiving SUTENT in GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in GIST or MRCC patients included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. In GIST Study A, 14/202 patients (7%) receiving SUTENT 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. Most events in MRCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5/202 patients (3%) with GIST receiving SUTENT 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 SUTENT.

5.6 Hypothyroidism

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of hypothyroidism on SUTENT treatment. Patients with signs or symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Treatment-emergent acquired hypothyroidism was noted in eight GIST patients (4%) on SUTENT versus one (1%) on placebo. Hypothyroidism was reported as an adverse reaction in eleven patients (3%) on SUTENT in the treatment-naïve MRCC study and in one patient (<1%) in the IFN-α arm. An additional seven patients (2%) with no prior history of hypothyroidism were started on thyroid replacement therapy while on study.

5.7 Adrenal Function

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

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.

5.8 Laboratory Tests

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

6 ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 577 patients who participated in a placebo-controlled trial (n=202) for the treatment of GIST or an active-controlled trial (n=375) for the treatment of MRCC. In these two studies, 225 patients were exposed to SUTENT for at least 6 months and 16 were exposed for greater than one year. The population was 23 - 87 years of age and 69% male and 31% female. The race distribution was 92% White, 3% Asian, 2% Black and 3% not reported. The patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST or MRCC are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia, and bleeding. The potentially serious adverse reactions of left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, and adrenal function are discussed in *Warnings and Precautions (5)*. Other adverse reactions occurring in GIST and MRCC studies are described below.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Reactions in GIST Study A

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. The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 7% and 6% in the SUTENT and placebo groups, respectively.

Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 56% versus 51% of patients on SUTENT versus placebo, respectively. Table 1 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT and reported more commonly in patients receiving SUTENT than in patients receiving placebo.

Table 1. Adverse Reactions Reported in Study A in at Least 10% of GIST Patients who Received SUTENT and More Commonly Than in Patients Given Placebo*

Adverse Reaction, n (%)	GIST			
	SUTENT (n=202)		Placebo (n=102)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any		114 (56)		52 (51)
Gastrointestinal				
Diarrhea	81 (40)	9 (4)	27 (27)	0 (0)
Mucositis/stomatitis	58 (29)	2 (1)	18 (18)	2 (2)
Constipation	41 (20)	0 (0)	14 (14)	2 (2)
Cardiac				
Hypertension	31 (15)	9 (4)	11 (11)	0 (0)
Dermatology				
Skin discoloration	61 (30)	0 (0)	23 (23)	0 (0)
Rash	28 (14)	2 (1)	9 (9)	0 (0)
Hand-foot syndrome	28 (14)	9 (4)	10 (10)	3 (3)
Neurology				
Altered taste	42 (21)	0 (0)	12 (12)	0 (0)
Musculoskeletal				
Myalgia/limb pain	28 (14)	1 (1)	9 (9)	1 (1)
Metabolism/Nutrition				
Anorexia[a]	67 (33)	1 (1)	30 (29)	5 (5)
Asthenia	45 (22)	10 (5)	11 (11)	3 (3)

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

[a] Includes decreased appetite

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.

Table 2 provides common (≥10%) treatment-emergent laboratory abnormalities.

Table 2. Laboratory Abnormalities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo*

Laboratory Parameter, n (%)	GIST			
	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)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Total bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Cardiac				
Decreased LVEF	22 (11)	2 (1)	3 (3)	0 (0)
Renal/Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Potassium decreased	24 (12)	1 (1)	4 (4)	0 (0)
Sodium increased	20 (10)	0 (0)	4 (4)	1 (1)
Hematology				
Neutrophils	107 (53)	20 (10)	4 (4)	0 (0)
Lymphocytes	76 (38)	0 (0)	16 (16)	0 (0)
Platelets	76 (38)	10 (5)	4 (4)	0 (0)
Hemoglobin	52 (26)	6 (3)	22 (22)	2 (2)

LVEF=Left ventricular ejection fraction

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

[a] Grade 4 laboratory abnormalities in patients on SUTENT included alkaline phosphatase (1%), lipase (2%), creatinine (1%), potassium decreased (1%), neutrophils (2%), hemoglobin (2%), and platelets (1%).

[b] Grade 4 laboratory abnormalities in patients on placebo included amylase (1%), lipase (1%) and hemoglobin (2%).

6.2 Adverse Reactions in the Treatment-Naïve MRCC Study

The as-treated patient population for the interim safety analysis of the treatment-naive MRCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 5.6 months (range: 0.4-15.6) for SUTENT treatment and 4.1 months (range: 0.1-13.7) on IFN-α treatment. Dose reductions occurred in 121 patients (32%) on SUTENT and 77 patients (21%) on IFN-α. Dose interruptions occurred in 142 patients (38%) on SUTENT and 115 patients (32%) on IFN-α. The rates of treatment-emergent, non-fatal adverse reactions resulting in permanent discontinuation were 9% and 12% in the SUTENT and IFN-α groups, respectively. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 67% versus 51% of patients on SUTENT versus IFN-α, respectively.

Table 3 compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Table 3. Adverse Reactions Reported in at Least 10% of Patients with MRCC Who Received SUTENT or IFN-α*

Adverse Reaction, n (%)	Treatment-Naïve MRCC			
	SUTENT (n=375)		IFN-α (n=360)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[b]
Any	370 (99)	250 (67)	354 (98)	184(51)
Constitutional				
Fatigue	218 (58)	35 (9)	199 (55)	50 (14)
Asthenia	79 (21)	27 (7)	85 (24)	20 (6)
Fever	62 (17)	3 (1)	129 (36)	0 (0)
Weight decreased	45 (12)	0 (0)	54 (15)	2 (1)
Chills	42 (11)	3 (1)	108 (30)	0 (0)
Gastrointestinal				
Diarrhea	218 (58)	22 (6)	72 (20)	0 (0)
Nausea	183 (49)	16 (4)	136 (38)	5 (1)
Mucositis/stomatitis	162 (43)	12 (3)	14 (4)	2 (<1)
Vomiting	105 (28)	15 (4)	51 (14)	3 (1)
Dyspepsia	105 (28)	4 (1)	14 (4)	0 (0)
Abdominal pain[c]	83 (22)	10 (3)	42 (12)	5 (1)
Constipation	60 (16)	0 (0)	44 (12)	1 (<1)
Dry mouth	45 (12)	0 (0)	26 (7)	1 (<1)
GERD/reflux esophagitis	42 (11)	0 (0)	3 (1)	0(0)
Flatulence	39 (10)	0 (0)	8 (2)	0 (0)
Oral pain	38 (10)	0 (0)	2 (1)	0 (0)
Glossodynia	37 (10)	0 (0)	2 (1)	0 (0)
Cardiac				
Hypertension	111 (30)	36 (10)	13 (4)	1 (<1)
Edema, peripheral	42 (11)	2 (1)	15 (4)	2 (1)
Dermatology				
Rash	103 (27)	3 (1)	40 (11)	2 (1)
Hand-foot syndrome	78 (21)	20 (5)	3 (1)	0 (0)
Skin discoloration/ yellow skin	72 (19)	0 (0)	0 (0)	0 (0)
Dry skin	67 (18)	1 (<1)	23 (6)	0 (0)
Hair color changes	56 (16)	0 (0)	1 (<1)	0 (0)
Neurology				
Altered taste[d]	166 (44)	1 (<1)	52 (14)	0 (0)
Headache	68 (18)	3 (1)	61 (17)	0 (0)
Dizziness	28 (7)	1 (<1)	42 (12)	1 (<1)
Musculoskeletal				
Back pain	70 (19)	13 (3)	44 (13)	6 (2)
Arthralgia	69 (18)	5 (1)	60 (17)	1 (<1)
Pain in extremity/ limb discomfort	65 (17)	6 (2)	28 (8)	4 (1)
Respiratory				
Cough	64 (18)	2 (1)	45 (12)	0 (0)
Dyspnea	58 (15)	15 (4)	65 (18)	14 (4)
Metabolism/Nutrition				
Anorexia[e]	142 (38)	6 (2)	145 (40)	7 (2)
Dehydration	30 (8)	8 (2)	17 (5)	2 (1)
Hemorrhage/Bleeding				
Bleeding, all sites	112 (30)	10 (3)[f]	27 (8)	2 (1)
Psychiatric				
Insomnia	42 (11)	1 (<1)	31 (9)	0 (0)
Depression[g]	29 (8)	0 (0)	47 (12)	5 (1)

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

[a] Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), asthenia (<1%), dehydration (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%).

[b] Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%) and depression (<1%).

[c] Includes flank pain

[d] Includes ageusia, hypogeusia and dysgeusia

[e] Includes decreased appetite

[f] Includes one patient with Grade 5 gastric hemorrhage

[g] Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented in Table 4.

Table 4. Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve MRCC Patients Who Received SUTENT or IFN-α

Laboratory Parameter, n (%)	Treatment-Naïve MRCC			
	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Gastrointestinal				
AST	195 (52)	6 (2)	124 (34)	6 (2)
ALT	171 (46)	10 (3)	140 (39)	6 (2)
Lipase	196 (52)	60 (16)	153 (43)	23 (6)
Alkaline phosphatase	156 (42)	7 (2)	126 (35)	6 (2)
Amylase	118 (31)	19 (5)	101 (28)	8 (2)
Total bilirubin	72 (19)	3 (1)	6 (2)	0 (0)
Indirect bilirubin	46 (12)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	246 (66)	1 (<1)	175 (49)	1 (<1)
Uric acid	155 (41)	43 (12)	112 (31)	29 (8)
Creatine kinase	152 (41)	1 (<1)	35 (10)	2 (1)
Phosphorus	134 (36)	17 (5)	115 (32)	22 (6)
Calcium decreased	132 (35)	1 (<1)	133 (37)	0 (0)
Glucose decreased	73 (19)	0 (0)	54 (15)	1 (<1)
Albumin	68 (18)	3 (1)	67 (19)	0 (0)
Glucose increased	58 (15)	10 (3)	49 (14)	20 (6)
Sodium decreased	51 (14)	18 (5)	41 (11)	9 (3)
Potassium increased	42 (11)	7 (2)	54 (15)	13 (4)
Sodium increased	40 (11)	0 (0)	35 (10)	0 (0)
Hematology				
Neutrophils	271 (72)	44 (12)	166 (46)	24 (7)
Hemoglobin	266 (71)	11 (3)	232 (64)	16 (4)
Platelets	244 (65)	30 (8)	77 (21)	0 (0)
Lymphocytes	223 (59)	44 (12)	227 (63)	79 (22)
Leukocytes	292 (78)	19 (5)	202 (56)	8 (2)

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

[a] Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (12%), lipase (3%), amylase (1%), neutrophils (1%), ALT (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), sodium decreased (<1%)and hemoglobin (<1%).

[b] Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lipase (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%).

6.3 Venous Thromboembolic Events

Seven patients (3%) on SUTENT and none on placebo in GIST Study A experienced venous thromboembolic events; five of the seven were Grade 3 deep venous thrombosis (DVT), and two were Grade 1 or 2. Four of these seven GIST patients discontinued treatment following first observation of DVT.

Eight (2%) patients receiving SUTENT for treatment-naïve MRCC had venous thromboembolic events reported. Four (1%) of these patients had pulmonary embolism, one was Grade 3 and three were Grade 4, and four (1%) patients had DVT, including one Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve MRCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, one Grade 1 and four with Grade 4.

6.4 Reversible Posterior Leukoencephalopathy Syndrome

There have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

6.5 Pancreatic and Hepatic Function

If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve MRCC compared to 1 (<1%) patient receiving IFN-α. Hepatic failure was observed in <1% of solid tumor patients treated with SUTENT.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT 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 plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*.

7.2 CYP3A4 Inducers

CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenob**arbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma** concentrations unpredictably. Patients receiving SUTENT should not take St. **John's Wort concomitantly. A dose increase for SUTENT should be considered** when it must be co-administered with CYP3A4 inducers *[see Dosage and Administration (2.2)]*.

7.3 In Vitro Studies of CYP Inhibition and Induction

In vitro studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.1)]*.

8.3 Nursing Mothers

Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The 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 (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) 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.

8.5 Geriatric Use

Of 825 GIST and MRCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Hepatic Impairment

No dose adjustment is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

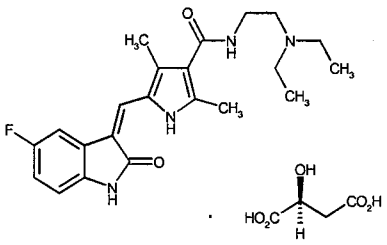
10 OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. 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/m^2) 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.

11 DESCRIPTION

SUTENT, an oral multi-kinase inhibitor, is the malate salt of sunitinib. 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-*3H*-indol-3-ylidine)methyl]-2,4-dimethyl-*1H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and the molecular weight is 532.6 Daltons.

The chemical structure of sunitinib malate is:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

SUTENT (sunitinib malate) 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.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The caramel gelatin capsule shells also contain yellow iron oxide and black iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis *in vivo*.

12.3 Pharmacokinetics

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors.

Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib. SUTENT may be taken with or without food.

Binding of sunitinib and its primary active metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration **dependence in the range of 100** – 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25 - 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose.

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of [^{14}C]sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged **from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of** sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

The pharmacokinetics were similar in healthy volunteers and in the solid tumor patient populations tested, including patients with GIST and MRCC.

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, race, gender, or ECOG score on the pharmacokinetics of SUTENT or the primary active metabolite.

Pediatric Use: The pharmacokinetics of SUTENT have not been evaluated in pediatric patients.

Renal Insufficiency: No clinical studies of SUTENT 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.**

Hepatic Insufficiency: Systemic exposures after a single dose of SUTENT were similar in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to subjects with normal hepatic function.

12.4 Cardiac Electrophysiology

See Warnings and Precautions (5.3).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with sunitinib have not been **performed, carcinoma and hyperplasia of the Brunner's gland of the duodenum** have been observed at the highest dose tested in H2ras transgenic mice administered doses of 0, 10, 25, 75, or 200 mg/kg/day for 28 days. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the 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.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 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 RDD], however significant embryolethality 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).

14 CLINICAL STUDIES

The clinical safety and efficacy of SUTENT have been studied in patients with gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate, and in patients with metastatic renal cell carcinoma (MRCC).

14.1 Gastrointestinal Stromal Tumor

Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The objective was to compare Time-to-Tumor Progression (TTP) in patients receiving SUTENT plus best supportive care versus patients receiving placebo plus best supportive care. Other objectives included Progression-Free Survival (PFS), Objective Response Rate (ORR), and Overall Survival (OS). Patients were randomized (2:1) to receive either 50 mg SUTENT or placebo orally, once daily, on Schedule 4/2 until disease progression or withdrawal from the study for another reason. Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label SUTENT, and patients randomized to SUTENT were permitted to continue treatment per investigator judgment.

The intent-to-treat (ITT) population included 312 patients. Two-hundred seven (207) patients were randomized to the SUTENT arm, and 105 patients were randomized to the placebo arm. Demographics were comparable between the SUTENT and placebo groups with regard to age (69% vs 72% <65 years for SUTENT vs. placebo, respectively), gender (Male: 64% vs. 61%), race (White: (88% both arms, Asian: 5% both arms, Black: 4% both arms, remainder not reported), and Performance Status (ECOG 0: 44% vs. 46%, ECOG 1: 55% vs. 52%, and ECOG 2: 1 vs. 2%). Prior treatment included surgery (94% vs. 93%) and radiotherapy (8% vs. 15%). Outcome of prior imatinib treatment was also comparable between arms with intolerance (4% vs. 4%), progression within 6 months of starting treatment (17% vs. 16%), or progression beyond 6 months (78% vs. 80%) balanced.

A planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a statistically significant advantage for SUTENT over placebo in TTP and progression-free survival. OS data were not mature at the time of the interim analysis. Efficacy results are summarized in Table 5 and the Kaplan-Meier curve for TTP is in Figure 1.

Table 5. GIST Efficacy Results from Study A (interim analysis)

Efficacy Parameter	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

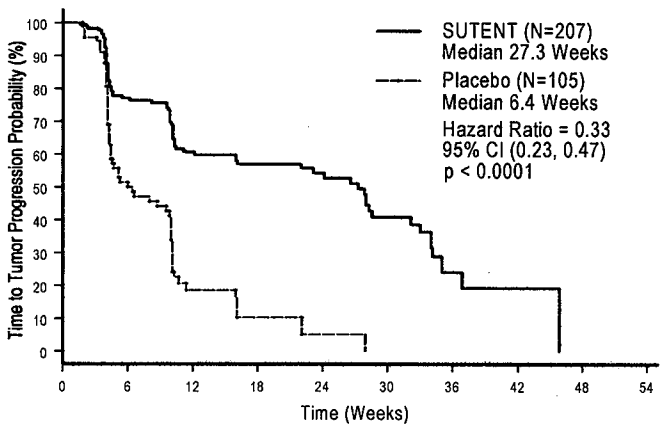
* A comparison is considered statistically significant if the p-value is < 0.0042 **(O'Brien Fleming stopping boundary)**

[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

Figure 1. Kaplan-Meier Curve of TTP in Study A (Intent-to-Treat Population)



Study B

Study B was an open-label, multi-center, single-arm, dose-escalation study conducted in patients with GIST following progression on or intolerance to imatinib. Following identification of the recommended Phase 2 regimen (50 mg once daily on Schedule 4/2), 55 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)].

14.2 Renal Cell Carcinoma

Treatment-Naïve MRCC

A multi-center, international randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naïve MRCC. The objective was to compare Progression-Free Survival (PFS) in patients receiving SUTENT versus patients receiving IFN-α. Other endpoints included Objective Response Rate (ORR), Overall Survival (OS) and safety. Seven hundred fifty (750) patients were randomized (1:1) to receive either 50 mg SUTENT once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MIU three times a week. Patients were treated until disease progression or withdrawal from the study.

The ITT population for this interim analysis included 750 patients, 375 randomized to SUTENT and 375 randomized to IFN-α. Demographics were comparable between the SUTENT and IFN-α groups with regard to age (59% vs. 67% <65 years for SUTENT vs. IFN-α, respectively), gender (Male: 71% vs. 72%), race (White: 94% vs. 91%, Asian: 2% vs. 3%, Black: 1% vs. 2%, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%, ECOG 1: 38% each arm, ECOG 2: 0 vs. 1%). Prior treatment included nephrectomy (91% vs. 89%) and radiotherapy (14% each arm). The most common site of metastases present at screening was the lung (78% vs. 80%, respectively), followed by the lymph nodes (58% vs. 53%, respectively) and bone (30% each arm); the majority of the patients had multiple (2 or more) metastatic sites at baseline (80% vs. 77%, respectively).

A planned interim analysis showed a statistically significant advantage for SUTENT over IFN-α in the endpoint of PFS (see Table 6 and Figure 2). In the pre-specified stratification factors of LDH (>1.5 ULN vs. ≤1.5 ULN), ECOG performance status (0 vs. 1), and prior nephrectomy (yes vs. no), the hazard ratio favored SUTENT over IFN-α. The ORR was higher in the SUTENT arm (see Table 6). OS data were not mature at the time of the interim analysis.

Table 6. Treatment-Naïve MRCC Efficacy Results (interim analysis)

Efficacy Parameter	SUTENT (n=375)	IFN-α (n=375)	P-value (log-rank test)	HR (95% CI)
Progression-Free Survival[a] [median, weeks (95% CI)]	47.3 (42.6, 50.7)	22.0 (16.4, 24.0)	<0.000001[b]	0.415 (0.320, 0.539)
Objective Response Rate[a] [%, (95% CI)]	27.5 (23.0, 32.3)	5.3 (3.3, 8.1)	<0.001[c]	NA

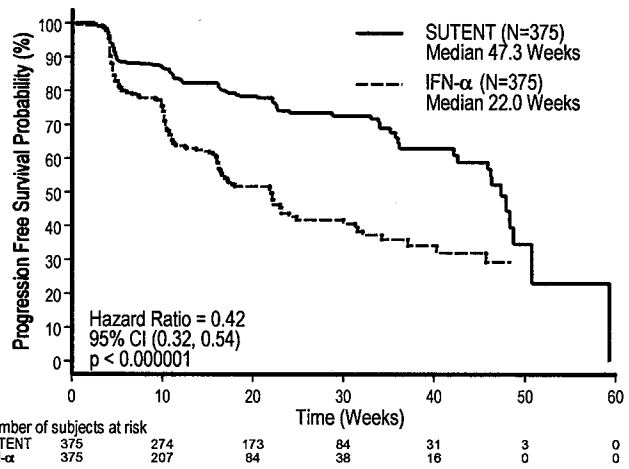
CI=Confidence interval, NA=Not applicable

[a] **Assessed by blinded core radiology laboratory; 90 patients' scans had not** been read at time of analysis

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

[c] Pearson Chi-square test

Figure 2. Kaplan-Meier Curve of PFS in Treatment-Naïve MRCC Study (Intent-to-Treat Population)



Cytokine-Refractory MRCC

The use of single agent SUTENT in the treatment of cytokine-refractory MRCC was investigated in two single-arm, multi-center studies. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In Study 1, failure of prior cytokine therapy was based on radiographic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (IFN-α, interleukin-2, or IFN-α plus interleukin-2; patients who were treated with IFN-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable treatment-related toxicity. The endpoint for both studies was ORR. Duration of Response (DR) was also evaluated.

One hundred six patients (106) were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients received 50 mg SUTENT on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were White. Men comprised 65% of the pooled population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status <2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

The ORR and DR data from Studies 1 and 2 are provided in Table 7. There were 36 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 34.0% (95% CI 25.0, 43.8). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI 24.7, 49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in Cycle 10. DR data from Study 1 is premature as only 9 of 36 patients (25%) responding to treatment had experienced disease progression or died at the time of the data cutoff.

Table 7. Cytokine-Refractory MRCC Efficacy Results

Efficacy Parameter	Study 1 (N=106)	Study 2 (N=63)
Objective Response Rate [%, (95% CI)]	34.0[a] (25.0, 43.8)	36.5[b] (24.7, 49.6)
Duration of Response (DR) [median, weeks (95% CI)]	* (42.0, **)	54[b] (34.3, 70.1)

CI=Confidence interval
* Median DR has not yet been reached
** Data not mature enough to determine upper confidence limit
[a] Assessed by blinded core radiology laboratory
[b] Assessed by investigators

16 HOW SUPPLIED/STORAGE AND HANDLING

12.5 mg Capsules

Hard gelatin capsule with orange cap and orange body, printed with white **ink "Pfizer" on the cap, "STN 12.5 mg" on the body; available in:**

Bottles of 28: NDC 0069-0550-38
Bottles of 30: NDC 0069-0550-30

25 mg Capsules

Hard gelatin capsule with caramel cap and orange body, printed with white **ink "Pfizer" on the cap, "STN 25 mg" on the body; available in:**

Bottles of 28: NDC 0069-0770-38
Bottles of 30: NDC 0069-0770-30

50 mg Capsules

Hard gelatin capsule with caramel cap and caramel body, printed with **white ink "Pfizer" on the cap, "STN 50 mg" on the body; available in:**

Bottles of 28: NDC 0069-0980-38
Bottles of 30: NDC 0069-0980-30

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See 17.5 for FDA-Approved Patient Labeling.

17.1 Gastrointestinal Disorders

Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

17.2 Skin Effects

Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

17.3 Other Common Events

Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

17.4 Concomitant Medications

Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions (7)]*.

17.5 FDA-Approved Patient Labeling

PATIENT INFORMATION

SUTENT (su TENT)

Read the patient information leaflet that comes with SUTENT before you start taking it. Read the leaflet each time you get a refill. There may be new information. This leaflet does not replace talking with your doctor about your condition or treatment. If you have any questions about SUTENT, ask your doctor or pharmacist.

What is the most important information I should know about SUTENT?

- **SUTENT may harm an unborn baby (cause birth defects).** Do not become pregnant. If you do become pregnant, tell your doctor right away. Stop taking SUTENT.

What is SUTENT?

SUTENT is a medicine that treats 2 kinds of cancer.

1. **GIST (gastrointestinal stromal tumor).** This is a rare cancer of the stomach, bowel, or esophagus. SUTENT is used when the medicine Gleevec® (imatinib mesylate) did not stop the cancer from growing OR when you cannot take Gleevec®.
2. **Advanced kidney cancer** (advanced renal cell carcinoma or RCC).

SUTENT may slow or stop the growth of cancer. It may help shrink tumors.

SUTENT has not been studied in children.

What should I tell my doctor before taking SUTENT?

Tell your doctor about all your medical conditions. **Be sure to tell your doctor if you:**

- are pregnant, could be pregnant, or plan to get pregnant. SUTENT may harm an unborn baby.
- are breast-feeding. Do not breast-feed while you are being treated with SUTENT.
- have any heart problems
- have high blood pressure
- have kidney function problems (other than cancer)
- have liver problems
- have any bleeding problem
- have seizures

SUTENT and other medicines

Tell your doctor about all your medicines. Include **prescription medicines,** over-the-counter drugs, vitamins, and herbal products. Some medicines can react with SUTENT and cause serious side effects.

Especially tell your doctor if you take:

- **St. John's Wort.** ***Do not take St. John's Wort while taking SUTENT.***
- Dexamethasone (a steroid)
- Medicine for:
  - **tuberculosis (TB)**
  - **infections (antibiotics)**
  - **depression**
  - **seizures (epilepsy)**
  - **fungal infections (antifungals)**
  - **HIV (AIDS)**

Keep a list of your medicines. Show it to your doctor or pharmacist. Talk with your doctor before starting any new medicines.

What are possible side effects of SUTENT?

Possible serious side effects include:

- **Heart Problems.** Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles.
- **Rare life-threatening events:** hole in stomach or bowel wall (perforation) or bleeding from the tumor. Both of these side effects could cause symptoms such as painful, swollen abdomen, vomiting blood, and black, sticky stools. Your doctor can tell you other symptoms to watch for.
- **Increased blood pressure.** Your doctor may check your blood pressure. You may need treatment for high blood pressure.

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Rx only

Common side effects:

- Feeling tired
- Diarrhea, nausea, vomiting, mouth sores, upset stomach, abdominal pain, and constipation. Talk with your doctor about ways to handle these problems.
- The medicine in SUTENT is yellow, so it may make your skin look yellow. Your skin and hair may get lighter.
- Your skin may become dry, get thicker, or crack. You may get blisters or a rash on the palms of your hands and soles of your feet.
- Taste changes
- Loss of appetite
- **Swelling**
- **High blood pressure**
- Bleeding, such as nosebleeds or bleeding from cuts. Call your doctor if you have any swelling or bleeding.

There are other side effects. For a more complete list, ask your cancer specialist nurse or doctor.

How should I take SUTENT?

- SUTENT comes in 12.5 mg, 25 mg, and 50 mg capsules you take by mouth. Do not open the capsules.
- Take SUTENT once a day with or without food.
- Take it exactly the way your doctor tells you.
- Do not drink grapefruit juice or eat grapefruit. They may change the amount of SUTENT in your body.
- Dosing cycle:
  - Take SUTENT for 4 weeks (28 days) THEN
  - Stop for 2 weeks (14 days)
  - Repeat this cycle as long as your doctor tells you
- Your doctor may check your blood before each dosing cycle.
- If you miss a dose, take it as soon as you remember. Do not take it if it is close to your next dose. Just take the next dose at your regular time. Do not take more than 1 dose of SUTENT at a time. Tell your doctor or nurse about the missed dose.
- Call your doctor right away, if you take too much SUTENT.

How do I store SUTENT?

- Keep SUTENT and all medicines out of the reach of children.
- Store SUTENT at room temperature.

General information about SUTENT

Doctors can prescribe medicines for conditions that are not in this patient information leaflet. Use SUTENT only for what your doctor prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them.

This leaflet gives the most important information about SUTENT. For more information about SUTENT, talk with your doctor or pharmacist. You can visit our website at www.SUTENT.com, or call 1-800-XXX-XXXX.

What is in SUTENT?

Active ingredient: sunitinib malate
Inactive ingredients: mannitol, croscarmellose sodium, povidone (K-25), magnesium stearate **Orange gelatin capsule shell:** titanium dioxide, red iron oxide **Caramel gelatin capsule shell:** yellow iron oxide, black iron oxide **Printing ink:** shellac, propylene glycol, sodium hydroxide, povidone, titanium dioxide

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

SUMMARY REVIEW

Division Director Summary Review of a Efficacy and Labeling Supplements

NDA 21-938/S-002/S-003/S-004/S-005
NDA 21-968/S-002/S-003/S-004/S-005/S-006
Drug: SUTENT® (sunitinib malate) Capsules
Applicant: CP Pharmaceuticals International CV (Pfizer, Inc.)
Date: February 2, 2007

On January 26, 2006, sunitinib was given full approval for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and accelerated approval for the treatment of advanced renal cell cancer.

NDA 21-938/S-002 and NDA 21-968/S-002 were submitted in response to postmarketing commitment #7 from the January 26, 2006, approval letter, and provide for revisions to the labeling based on data from the study titled, *"A Phase 1 Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors"*.

NDA 21-938/S-003 and NDA 21-968/S-003 and S-004 were submitted in response to postmarketing commitments #1 and #3 from the January 26, 2006, approval letter and provide for revisions to the labeling based on data from the first interim efficacy and safety analysis for 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"*. The supplements also provide the datasets containing the core imaging facility assessments used to derive the updated response rate for the study titled, *"A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma"*.

NDA 21-938/S-004 and NDA 21-968/S-005 were submitted in response to postmarketing commitments #2 and #4 from the January 26, 2006, approval letter and provide for revisions to the labeling based on data from the final study report for 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"*. The supplements also provide follow-up left ventricular ejection fraction (LVEF) data for selected patients on the study titled, *"A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma"*.

NDA 21-938/S-005 and NDA 21-968/S-006 were submitted in response to postmarketing commitment #8 from the January 26, 2006, approval letter and provide for revisions to the labeling based on data from the final study report for the study titled, *"A Phase I Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function"*.

Clinical Review

The Clinical Review by Vicki Goodman, M.D. summarizes the clinical program and the efficacy and safety results:

1.3.1 Brief Overview of Clinical Program

Sunitinib received accelerated approval for the treatment of advanced renal cell carcinoma on January 26, 2006 based on durable partial responses in two single-arm studies performed in patients with cytokine-refractory renal cell carcinoma. At the time of approval, a confirmatory randomized study comparing progression-free survival in patients receiving sunitinib to patients receiving IFN-α was ongoing (study A6181034). The current submissions provide updated response data from the larger of the two single-arm studies (A6181006), as well as response data and progression-free survival data from interim analyses of study A6181034. The progression-free survival data is intended to serve as confirmation of clinical benefit in patients with advanced renal cell carcinoma.

1.3.2 Efficacy

Study A6181034 is a randomized, open label trial in patients with treatment-naïve metastatic renal cell carcinoma. Seven hundred and fifty patients were randomized 1:1 to receive either sunitinib or IFN-α. Sunitinib was given at a starting dose of 50 mg orally once daily for 4 weeks, followed by a two week rest period (4/2 schedule). IFN-α was given subcutaneously on three nonconsecutive days per week at a starting dose of 3 MU per dose during the first week, 6 MU per dose the second week and 9 MU per dose thereafter.

Three hundred and seventy-five patients were randomized to each arm. The two treatment arms were well balanced for baseline demographic characteristics, including age, gender, and race. Patients were required to have some component of clear cell histology and most (90%) had undergone prior nephrectomy. The median number of sites of disease was two: common sites included lung, lymph nodes, bone and liver.

The primary endpoint was progression-free survival (PFS), defined as the time from randomization to documented progression or death. Patients who had not progressed or died were censored on the day following the date of the last on study, which included a 28 day follow-up period after dosing was discontinued. For the primary analysis of PFS in the intent-to-treat (ITT) population based on independent review data, there were 96 events (25.6%) of progression or death on the sunitinib arm compared with 154 events (41.1%) of progression or death on the IFN arm. Median PFS was 47.3 weeks (95% CI 42.6, 50.7) for sunitinib-treated patients and 22.0 weeks (95% CI 16.4, 24.0) for patients treated with IFN; the hazard ratio was 0.415 (95% CI .320, 0.539, $p<0.000001$). These results were

supported by three sensitivity analyses of PFS. Overall survival data were not mature at the time of this analysis.

Overall response rate was higher on the sunitinib arm compared to the IFN arm, with an ORR of 27.5% (95% CI 23.0%, 32.3%) vs. 5.3% (95% CI 3.3%, 8.1%). The response rate noted on the sunitinib arm is similar to the response rates seen in two single-arm trials of sunitinib in patients with cytokine-refractory MRCC.

The updated response data from study A6181006 include an ORR (all partial responses) of 34% (95% CI 25.0, 43.8) as evaluated by the core radiology laboratory, which was the protocol-specified primary analysis. Duration of response data are not mature (the median has not been reached with nine failures and 27 censored patients); the lower bound of the 95% CI was reported as 42 weeks.

1.3.3 Safety

Common drug-related adverse events included GI events [diarrhea (58% sunitinib vs. 20% IFN-α), nausea (49% vs. 38%), mucositis (43% vs. 4%), vomiting (28% vs. 14%), dyspepsia (28% vs. 4%), abdominal pain (22% vs. 12%), gastroesophageal reflux (11% vs. 1%), oral pain (10% vs. 1%), glossodynia (10% vs. 1%) and flatulence (10% vs. 2%)], bleeding (30% vs. 8%), hypertension (30% vs. 4%), dermatologic events [rash (27% vs. 11%), skin discoloration (19% vs. 0%), dry skin (18% vs. 6%), and hair color changes (15% vs. <1%)], palmar-plantar erythrodysesthesia (21% vs. 1%), limb pain (17% vs. 8%), decreases in cardiac ejection fraction (12% vs. 5%), and peripheral edema (11% vs. 4%). Although the incidence of fatigue is not higher in patients treated with sunitinib, the similarity in incidence of fatigue to patients treated with IFN (58% vs. 55%), a well known cause of fatigue, makes it likely that fatigue is also related to sunitinib.

Grade 3/4 adverse events more common on the sunitinib arm included hypertension (10% vs. <1%), diarrhea (6% vs. 0%), palmar-plantar erythrodysesthesia (5% vs. 0%), nausea (4% vs. 1%), vomiting (4% vs. 1%), mucositis (3% vs. 1%), and bleeding (3% vs. 1%).

Less common adverse events that are likely drug related include pharyngeolaryngeal pain (9% vs. 2%), paresthesias (8% vs. 1%), erythema (8% vs. 1%), hemorrhoids (7% vs. 1%), facial edema (7% vs. 1%), nasopharyngitis (7% vs. 1%), skin exfoliation (7% vs. 1%), neuropathy (6% vs. 3%), pleural effusion (5% vs. 1%), lacrimation increased (5% vs. 0%), dysphonia (5% vs. 1%), chromaturia (4% vs. <1%), dysphagia (4% vs. 1%), and hypothyroidism (3% vs. <1%).

Patients receiving sunitinib were more likely to develop significant changes in LVEF and/or clinical evidence of ventricular dysfunction. Thirteen patients on sunitinib (4%) and four on IFN-a (1%) experienced declines in LVEF of > 20%

from baseline and to below 50%. One patient who received sunitinib was diagnosed with congestive heart failure and three patients were diagnosed with left ventricular dysfunction.

Grade 3/4 laboratory abnormalities which are more common in sunitinib-treated patients include hematologic abnormalities [neutropenia (12% vs. 7%), thrombocytopenia (8% vs. 0%), and leucopenia (5% vs. 2%)], increased lipase (15% vs. 5%), increased amylase (4% vs. 2%), hyponatremia (5% vs. 2%), hyperuricemia (10% vs. 4%) and hyperbilirubinemia (1% vs. 0%).

Dr. Goodman made the following 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 conversion of this application for sunitinib for the treatment of advanced renal cell carcinoma (RCC) to regular approval. This recommendation is based on a clinically and statistically robust improvement in progression-free survival in a randomized trial of patients receiving sunitinib as first-line treatment of metastatic renal cell carcinoma (MRCC) compared to those patients receiving interferon-α (IFN-α).

The review made the following comments regarding the required phase 4 commitments:

The subpart H phase 4 commitments confirming clinical benefit have been fulfilled with these supplements. The sponsor has also fulfilled the commitment to provide additional data relating to patients with abnormal left ventricular ejection fraction from study A6181006.

There is one remaining outstanding required phase 4 commitment from the initial NDA approval:

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

FDA, Pfizer and NCI (the sponsor of this ECOG study) have discussed and implemented a sub-study design to further characterize changes in left ventricular ejection fraction in patients receiving sunitinib compared to those receiving placebo. It is anticipated that data from this sub-study will be available in 2011.

Additionally, one prior commitment, to provide efficacy data from study A6181034 has been partially fulfilled. The commitment required data including PFS, ORR, duration of response and OS to be submitted. While ORR and PFS data have been submitted, duration of response and OS data were not mature. The submission of these data, when mature, will be the subject of an additional PMC.

- The sponsor will submit the complete study report and datasets with the final statistical analysis of overall survival and duration of response for study A6181034.

Statistical Review and Evaluation

The Statistical Review and Evaluation by Shenghui Tang, Ph.D. provided the following conclusions and recommendations:

> On 10 August 2005, the sponsor submitted an application to evaluate the efficacy of single-agent SU011248 (Sunitinib, SUTENT®) in patients with progressive metastatic renal cell carcinoma who were refractory to 1 prior cytokine therapy (IFN, IL-2, or IFN + IL-2). The application was for accelerated approval and the primary efficacy endpoint was the objective response rate (ORR). It was based primarily on data from the Phase II pivotal study, A6181006. Supportive data were provided from the Phase II study (RTKC-0511-014) in the same patient population. The FDA granted accelerated approval for Sunitinib (SUTENT®) on 26 January 2006 for advanced renal cell carcinoma (RCC).
>
> For the purpose of converting the accelerated approval to a regular approval, the sponsor submitted efficacy and safety data from a confirmatory Study A6181034, "A Phase 3, Randomized Study of SU011248 versus Interferon-α (IFN-α) as First Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma". The submission No. 003 included an interim analysis for ORR and the submission No. 005 included an interim analysis for Progression-Free Survival (PFS).
>
> Primary efficacy analysis of Study A6181034 is PFS analysis for the ITT population as assessed by the independent imaging core laboratory. At the time of data cutoff for the interim PFS analysis (15 November 2005), 750 subjects were randomized: 375 in the Sunitinib arm and 375 in the IFN-α arm. The PFS analysis included 96 events (25.6%) for PFS in the Sunitinib arm and 154 events (41.1%) for PFS in the IFN-α arm. Estimated medians of PFS in the Sunitinib arm and the IFN-α arm were 47.3 weeks and 22.0 weeks respectively. The hazard ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm, was 0.415 (p-value < 0.000001).
>
> At the time of PFS analysis, the analysis for the ORR based on the core imaging laboratory results identified 103 (27.5%) versus 20 (5.3%) partial responses on Sunitinib versus IFN-α, respectively; of these subjects, 16 (15.5% subjects with responses) vs. 0 (0.0% subjects with responses) subsequently progressed or died. Median duration of response (DR) was 40.9 weeks (95% CI: 30. 1 to 54.1 weeks) on Sunitinib. Duration of response on IFN-α could not be calculated because no subjects had subsequent progression or death.
>
> The submitted data support the claim based on PFS analysis. Whether the endpoint and the size of the effect on the primary endpoint in Study A6181034 are

adequate for converting the accelerated approval to a regular approval is deferred to clinical judgment.

Clinical Inspection Summary

The Clinical Inspection Summary by J. Lloyd Johnson, Pharm.D. concluded the following:

> In general, for the two study sites inspected, it appears that sufficient documentation to assure that study subjects audited at those two sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Clinical Pharmacology and Biopharmaceutics Review

The Clinical Pharmacology and Biopharmaceutics Review was completed by Roshni Ramchandani, Ph.D. The following is an excerpt from the executive summary:

> The current submission is a supplemental NDA for sunitinib. It includes two clinical study reports and a data analysis report submitted in fulfillment of the following phase 4 commitments: 1) evaluation of the effect of sunitinib on QTc interval, 2) evaluation of pharmacokinetics of sunitinib subjects with impaired hepatic function, 3) exposure-response analyses of sunitinib in treatment-naïve and cytokine refractory renal cell carcinoma patients in phase 2 and 3 clinical studies.
>
> The results of the QTc study indicated that at therapeutic concentrations, sunitinib prolongs the QT interval. The results of the hepatic impairment study indicated that mean Cmax and AUC for sunitinib and its primary active metabolite, SU012662, were similar between subjects with mild and moderate hepatic impairment and normal subjects. Exposure-efficacy analyses were performed to evaluate the relationship between sunitinib exposure (AUC) and three measures of efficacy, time to tumor progression, response rates and changes in tumor size. Data was pooled across the studies in cytokine-refractory and treatment-naïve patients. There was no significant relationship between AUC and time to tumor progression or death, possibly due to the small number of patients with observed data among the treatment-naïve patients. Analysis of response rates showed a significant correlation of AUC of sunitinib with the probability of a partial response in cytokine-refractory patients.

The review made the following recommendations:

> The Office of Clinical Pharmacology finds the studies submitted by the applicant to be acceptable, and in fulfillment of the applicant's post-marketing commitments as described below.

Post marketing commitments:
1. Submit the completed report and datasets for study titled "A phase 1 study to evaluate the effect of SU011248 on QTc interval in subjects with advanced solid tumors" (PMC #7).

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" (PMC #8).

3. Provide an analysis of the relationship between exposure and efficacy outcomes from the study titled "A phase 3, randomized study of SU011248 versus Interferon-a as first-line systemic therapy for patients with metastatic renal cell carcinoma" (PMC #6).

Study Endpoints and Label Development Team Consult

Since the revised label is in PLR format, a SEALD consultation was obtained from Iris Masucci, Pharm.D. Dr. Masucci's comments were addressed during the labeling discussions.

OSE/DSRCS Consultation

An OSE/DSRCS consultative review of the patient labeling was completed by Jeanine Best, M.S.N., R.N., P.N.P. The recommended changes to the patient labeling were made.

DDMAC Consultation

A DDMAC consultation on the labeling was completed by Kathy Oh and the recommendations were discussed during the labeling discussions.

Interdisciplinary Review Team for QT Studies

The IRT consultation on the TQT study made the following general comments:

1. Of the 48 patients enrolled, 44 (92%) patients completed the full protocol-specified treatment regimen, but only 24 (50%) patients were included in the evaluable population. It should be noted that the study power was based on a sample size of 24 subjects if the evaluable population is the primary population for analysis.

2. It needs to be pointed out that the study design consists of only one sequence of crossover treatment. It is a single blind study with patients receiving the treatment with a non-randomized assignment. Because of the limitation of the study, one cannot separate the treatment effects from the period effects.

3. According to the protocol, "To exclude a 10 ms QT/QTc prolongation for this study, if the upper bound of the 95% one-sided (90% two-sided) confidence limits for study drug minus placebo are below —ms, SU011248 will be deemed to have no clinically significant effect in this population on the QT/QTc interval." Please explain the rationale of choosing an upper bound of — ms. b(4)

4. The timing of ECG measurements was inadequate because the peak QTc effect was not observed. Sampling for PK and ECGs on day 3 and 9 was conducted for 24 hrs following dosing. While additional samples were collected at 72 hrs and 168 hrs after the day 9 dose, these time points were not included in the QTc analysis. Given the time delay between concentrations and QTc changes and that most patients showed maximal changes at the 24 hr time point, it would have been helpful to have additional data points beyond 24 hrs for a more complete characterization of the time course of QTc changes. In current ongoing studies with Sutent, the sponsor should collect ECGs after at least two half lives after pharmacokinetic steady state has been reached, in order to capture the maximum effect of drug on the QTc interval.

The following summary of findings was provided in the consultation:

The sponsor conducted a thorough QT study to evaluate the QT prolongation potential of sunitinib at therapeutic and supratherapeutic concentrations in advanced solid tumor patients. Results indicate a maximum mean placebo-adjusted change in QTcF of 14.5 msec, with a 90% CI of 9.5 – 19.5 msec at therapeutic concentrations, and a change in QTcF of 20.3 msec with a 90% CI of 13.4 – 27.1 msec at supratherapeutic concentrations (~2x therapeutic concentrations).

The sponsor has included information in the Warnings and Precautions as well as the Clinical Pharmacology sections of the product label (see section 7).

In addition, the reviewers have noted a Medwatch report of torsade de pointes (TdP), sent to the Oncology Division on July 7, 2006. This report involves a 47 year old male receiving open-sunitinib for renal cell carcinoma. This patient developed vomiting and diarrhea, followed by cardiac arrest (successfully resuscitated) and focal seizures. On examination, he was noted to have ventricular tachycardia, TdP and long QT (we do not have the tracings). Concomitant medications included: gabapentin, morphine, prozac, zopiclone, and propranolol. Magnesium, potassium, sodium and calcium were all reportedly normal (we do not have the actual values).

The risk of QT prolongation and the report of torsade de pointes were included in the revised labeling along with the precautions to be taken.

Recommendation

Based on the data summarized in the reviews by Drs. Goodman and Tang, I concur that the results of Study A6181034 warrant the conversion of the advanced renal cell cancer NDA (21-968) from accelerated to full approval. Agreement has been reached with the applicant on the revised label and the efficacy and labeling supplements should be approved. The approval letter should state that the following subpart H postmarketing commitments have been fulfilled:

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 raw and derived datasets containing the core imaging facility assessments used to derive the updated response rate and 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.

The following additional non-Subpart H postmarketing commitments have also been fulfilled:

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 QTc Interval in Subjects 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".

The following subpart H postmarketing study commitment should be converted to a regular postmarketing study commitment:

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.

Initial Protocol Submission:	submitted 11/2005
Revised Protocol Submission:	by 05/2006
Study Start:	by 03/2006
Final Report Submission:	by 06/2011

Finally, the sponsor agreed to the following new postmarketing study commitment:

1. Provide the complete study report and datasets with the final definitive statistical analysis of overall survival and duration of response for the study titled, "A Phase 3, Randomized Study of SU011248 versus Interferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

Protocol Submission:	submitted 6/2004
Study Start:	8/2004
Final Report Submission:	2/2009

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
2/2/2007 07:10:36 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

CROSS DISCIPLINE TEAM LEADER REVIEW

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: NDA Review

NDA	21938
Brand Name	SUTENT®
Generic Name	Sunitinib
Sponsor	Pfizer Inc.
Indication	(1) Treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate. (2) Treatment of advanced renal cell carcinoma (RCC).
Dosage Form	Capsules for oral administration
Therapeutic Dose	50 mg once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (schedule 4/2)
Duration of Therapeutic Use	Administered until disease progression or unacceptable toxicity
Maximum Tolerated Dose	75 mg QD
Application Submission Date	30-Mar-2006
Review Classification	Other
Date Consult Received	3-Oct-2006
Date Consult Due	15-Dec-2006
Clinical Division	Division of Drug Oncology Products
PDUFA Date	3-Feb-2007

1 RECOMMENDATION

1.1 Labeling:

The sponsor has included the following information in the SUTENT label regarding QT interval prolongation:

In the HIGHLIGHTS Section:
WARNINGS AND PRECAUTIONS

- Prolonged QTc intervals occurred at therapeutic concentrations. Torsade de Pointes has been observed [redacted]. Use with caution in patients at higher risk for developing QT interval prolongation. [redacted] (5.3)

b(4)

In the Full Prescribing Information:
Under WARNINGS AND PRECAUTIONS SECTION:
5.3 QT Interval Prolongation

[redacted]

b(4)

b(4)

SUTENT has been shown to prolong the QTcF interval, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients. SUTENT should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered (see *Dose Modification [2.2]*).

b(4)

In the CLINICAL PHARMACOLOGY SECTION:

12.4 Cardiac Electrophysiology

See section 5.3, QT interval prolongation, in section WARNINGS AND PRECAUTIONS

Reviewer Comments

Related to label

1. The confidence intervals listed above should be modified to include both lower and upper limits. Also, the CTCAE grade should be specified in terms of the actual change in msec.

2. In the Precaution and Warning section, we recommend adding the following sentence: When using SUTENT, should consider periodic monitoring of on-treatment electrocardiograms.

b(4)

3. Numbers in label should be changed to within-day baseline corrected values.

General comments

1. Of the 48 patients enrolled, 44 (92%) patients completed the full protocol-specified treatment regimen, but only 24 (50%) patients were included in the evaluable population. It should be noted that the study power was based on a sample size of 24 subjects if the evaluable population is the primary population for analysis.

2. It needs to be pointed out that the study design consists of only one sequence of crossover treatment. It is a single blind study with patients receiving the treatment with a non-randomized assignment. Because of the limitation of the study, one cannot separate the treatment effects from the period effects.

3. According to the protocol, "To exclude a 10 ms QT/QTc prolongation for this study, if the upper bound of the 95% one-sided (90% two-sided) confidence limits for study drug minus placebo are below — ms, SU011248 will be deemed to have no clinically significant effect in this population on the QT/QTc interval." Please explain the rationale of choosing an upper bound of — ms. b(4)

4. The timing of ECG measurements was inadequate because the peak QTc effect was not observed. Sampling for PK and ECGs on day 3 and 9 was conducted for 24 hrs following dosing. While additional samples were collected at 72 hrs and 168 hrs after the day 9 dose, these time points were not included in the QTc analysis. Given the time delay between concentrations and QTc changes and that most patients showed maximal changes at the 24 hr time point, it would have been helpful to have additional data points beyond 24 hrs for a more complete characterization of the time course of QTc changes. In current ongoing studies with Sutent, the sponsor should collect ECGs after at least two half lives after pharmacokinetic steady state has been reached, in order to capture the maximum effect of drug on the QTc interval.

2 SUMMARY OF FINDINGS

The sponsor conducted a thorough QT study to evaluate the QT prolongation potential of sunitinib at therapeutic and supratherapeutic concentrations in advanced solid tumor patients. Results indicate a maximum mean placebo-adjusted change in QTcF of 14.5 msec, with a 90% CI of 9.5 – 19.5 msec at therapeutic concentrations, and a change in QTcF of 20.3 msec with a 90% CI of 13.4 – 27.1 msec at supratherapeutic concentrations (~2x therapeutic concentrations).

The sponsor has included information in the Warnings and Precautions as well as the Clinical Pharmacology sections of the product label (see section 7).

In addition, the reviewers have noted a Medwatch report of torsade de pointes (TdP), sent to the Oncology Division on July 7, 2006. This report involves a 47 year old male receiving open-label sunitinib for renal cell carcinoma. This patient developed vomiting and diarrhea, followed by cardiac arrest (successfully resuscitated) and focal seizures. On examination, he was noted to have ventricular tachycardia, TdP and long QT (we do not have the tracings). Concomitant medications included: gabapentin, morphine, prozac, zopiclone, and propranolol. Magnesium, potassium, sodium and calcium were all reportedly normal (we do not have the actual values).

3 GOAL OF THE REVIEW

The purpose of this review is to assess the impact of sunitinib on QT interval based on the study conducted in patients with advanced solid tumors.

4 BACKGROUND

4.1 Indication

(1) Treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.
(2) Treatment of advanced renal cell carcinoma (RCC).

4.2 Drug Class

Sunitinib malate (SU011248) is a small molecule, multi-targeted receptor tyrosine kinase inhibitor. It selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinases (RTKs).

4.3 Market approval status

Sunitinib was approved in January 2006 for the treatment of GIST and given accelerated approval for advanced renal cell cancer. The sponsor is currently seeking conversion of the accelerated approval to traditional approval of sunitinib for advanced renal cell cancer.

The current submission is in fulfillment of one of the phase IV commitments made at the time of approval, to submit the complete report of their study evaluating the effect of sunitinib on QT interval in patients with advanced solid tumors.

5 DRUG INFORMATION

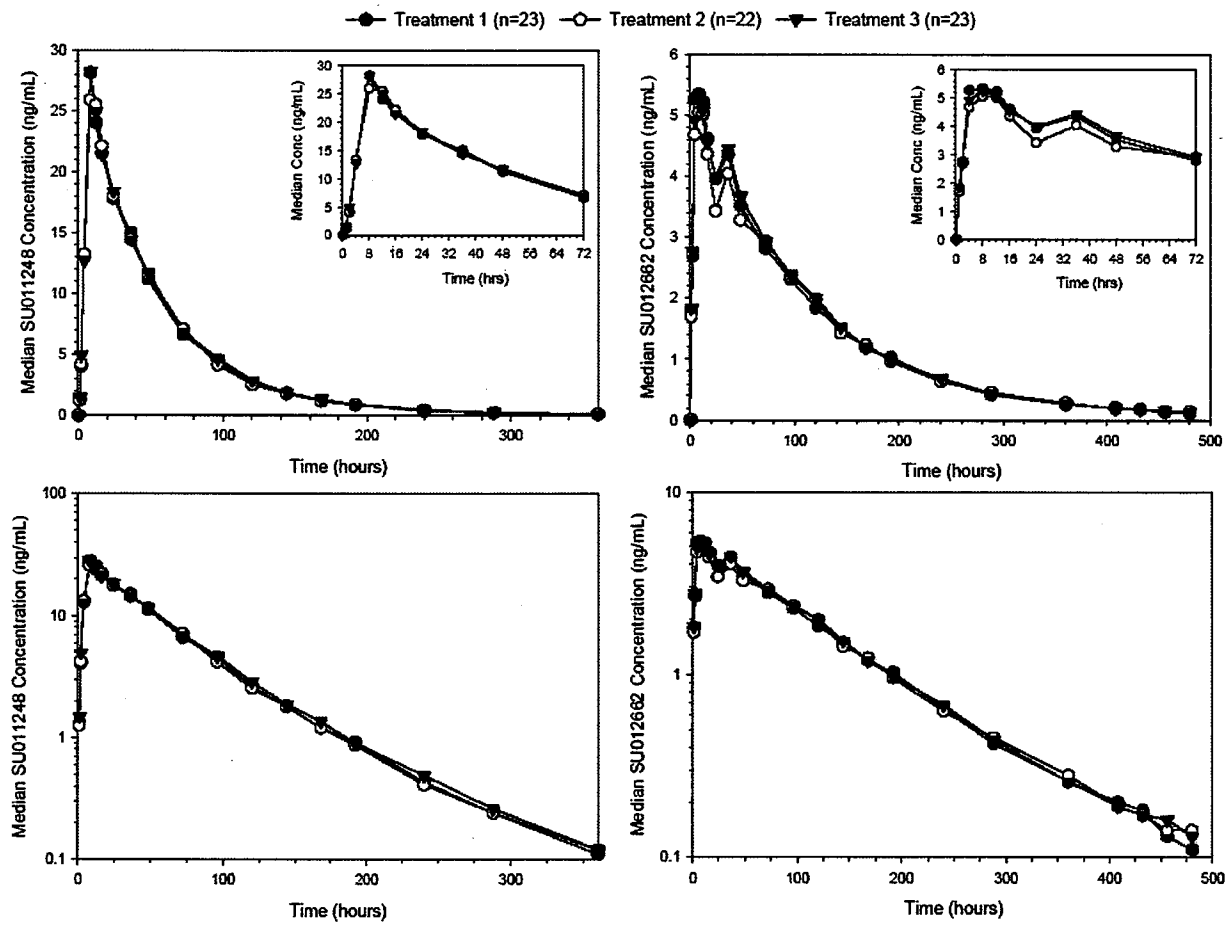
5.1 Preclinical Information

Pre-clinical safety pharmacology studies, *in vivo* and *in vitro*, identified potential cardiac conduction system issues. The *in vitro* studies indicated that SU011248 (IC_{50} = 266 nM =108 ng/mL) and its active metabolite SU012662 (IC_{50} > 4100 μM ≈ 1500 μg/mL) blocked the hERG potassium ion channel (I_{Kr}). A cardiovascular study in monkeys given high single doses (50 and 150 mg/kg) of SU011248 demonstrated heart rate corrected QT interval (QTc) prolongation.

5.2 Clinical Pharmacology

Figure 1 illustrates the pharmacokinetics of sunitinib following single 50 mg doses (3 different formulations). Table 1 summarizes the key features of the clinical pharmacology of sunitinib.

Figure 1. Plasma Concentration vs. Time Profiles for Sunitinib (SU011248) and SU012662 Following Single 50 mg Doses of Three Different Formulations.



Source: A6181033 CSR, Figure 1, Figures 14.2.1.1, 14.2.1.2, 14.2.2.1, 14.2.2.2.
Note: Treatment 1 = 50-mg clinical trial formulation of sunitinib, Treatment 2 = 50-mg proposed commercial formulation of sunitinib, Treatment 3 = 4 × 12.5-mg proposed commercial formulation of sunitinib.
The inset plots show an expanded view of the 0-72 hour time period.
For sunitinib, median concentrations beyond 360 hours are not shown because concentrations were BLQ (<0.1 ng/mL).

Table 1. Highlights of Clinical Pharmacology of Sunitinib and its Primary Active Metabolite SU012662.

Therapeutic dose	50 mg daily for 4 weeks followed by a 2 week rest	
Maximum dose tested	Single Dose	350 mg
	Multiple Dose	100 mg QD
Exposures Achieved	Following recommended dose of 50 mg QD: Cmax,ss for sunitinib = 68.5-90.2 ng/ml Cmax,ss for SU012662 = 33.7-46.1 ng/ml AUC for sunitinib = 1262-1697 ng.hr/ml AUC for SU012662 = 592-844 ng.hr/ml	
Maximum tolerated dose	75 mg QD for 4 weeks	
Principal adverse events	fatigue, nausea, hypertension, mucositis, diarrhea	
Absorption	Absolute Bioavailability	not determined
	Tmax	sunitinib: 6-12 hrs SU012662: 6-12 hrs
Distribution	Vd/F	sunitinib: 2230 L
	% bound	sunitinib: 95% SU012662: 90%
Elimination	Route	hepatic metabolism via CYP3A4.
	Metabolite	Predominant metabolite SU012662 is equipotent with regard to tyrosine kinase inhibition. SU012662 comprises 23 to 37% of the total exposure.
	Terminal t½	sunitinib: 40-60 hrs SU012662: 80-110 hrs
	CL/F	sunitinib: 34-62 L/hr (%CV: 40%)
	Accumulation: $\frac{AUC24_{(Day\ 28)}}{AUC24_{(Day\ 1)}}$	sunitinib: 3.55 SU012662: 10.2
Range of linear PK	Dose proportional increases in AUC: 25 to 350 mg single doses in healthy subjects and 25-100 mg multiple doses in patients	
Intrinsic Factors	Age	No clinically significant age effects based on population PK analysis of data across studies
	Sex	No clinically significant sex effects based on population PK analysis of data across studies
	Race	No clinically significant race effects based on population PK analysis of data across studies
Extrinsic Factors	Drug interactions	• Both sunitinib and SU012662 are extensively metabolized by CYP3A4 so PK will be affected by inhibitors or inducers • DDI study with ketoconazole (CYP3A4 inhibitor) showed a 51% increase in

b(4)

		combined sunitinib+SU012662 AUC in presence of ketoconazole. • DDI study with rifampin (CYP3A4 inducer) showed 46% decrease in combined sunitinib+SU012662 AUC in presence of rifampin
	Food Effects	No effect of food on bioavailability.
High Clinical Exposure scenario	• Expected if co-administered with CYP3A4 inhibitors	

6 SPONSOR'S SUBMISSION

6.1 Overview

The sponsor submitted 1) the results of their evaluation of ECG changes in their phase 3 study comparing sunitnib vs. IFN in advanced renal cell cancer patients; and 2) a QTc study (A6181005) evaluating the effect of sunitinib on the QT interval in advanced solid tumor patients.

6.2 Evaluation of ECG data from pivotal study (A6181034)

The sponsor submitted the results of their pivotal phase 3 study comparing sunitinib vs. interferon (IFN) in patients with advanced renal cell cancer. As part of this study, ECGs were done at screening (baseline) and then on day 28 (at trough).

Additional ECGs were done as indicated. QTc results (Fridericia's correction) and change from baseline are summarized by day in Table 2.

Table 2. QTc Interval and Change from Baseline in QTc by Day for Sunitinib (upper panel) and IFN (lower panel).

	Study Period	N	Mean	Std	Minimum	Median	Maximum
Sunitinib							
QTc (Fridericia) (msec)	Baseline	371	400.0	26.0	266.0	400.7	481.5
	Cycle 1 Day 28	341	408.2	27.6	242.5	406.7	524.8
	Cycle 2 Day 1	2	417.5	4.9	414.0	417.5	421.0
	Cycle 2 Day 28	1	393.9		393.9	393.9	393.9
	Termination	1	445.8		445.8	445.8	445.8
Change from Baseline in QTc (Fridericia) (msec)	Cycle 1 Day 28	337	8.0	23.7	-95.4	6.9	117.3
	Cycle 2 Day 1	2	17.7	17.2	5.5	17.7	29.9
	Cycle 2 Day 28	1	8.5		8.5	8.5	8.5
	Termination	1	39.2		39.2	39.2	39.2
IFN							
QTc (Fridericia) (msec)	Baseline	358	398.8	27.8	288.4	399.6	488.0
	Cycle 1 Day 28	312	403.2	27.0	297.1	404.1	473.6
	Cycle 2 Day 1						
	Cycle 2 Day 28						
	Termination	2	422.3	9.2	415.8	422.3	428.8

Change from Baseline in QTc (Fridericia) (msec)	Cycle 1 Day 28	311	3.8	24.2	-85.6	2.5	116.3
	Cycle 2 Day 1						
	Cycle 2 Day 28						
	Termination	2	24.2	3.8	21.5	24.2	26.9

(Reproduced from Sponsor, Table 13.9.1, page 2945, Study A6181034 Study Report)

There was a mean 8 msec (Std: 23.7, range: -95.4 to 117.3) increase in QTcF from baseline across the sample for sunitinib (n=337) and a 3.8 msec (Std: 24.2, range: -85.6 to 116.3) increase in QTcF from baseline for IFN (n=311).

Table 3 summarizes the number of patients with various grades of QTc changes, as defined by NCI CTC version 3 (National Cancer Institute Common Toxicity Criteria, Bethesda, MD). The table indicates that 2.9% of sunitinib and 2.2% of IFN patients showed QTc between 470 and 500 msec or change in QTc greater than 60 msec.

Table 3. Number of Patients with Various Grades of QTc Changes in Sunitinib and IFN Arms of Study A6181005

Grade	Sunitinib Total N=375	IFN Total N=360
Grade 0: QTc < 450 msec	321 (85.6%)	292 (81.1%)
Grade 1: QTc > 450 - 470 msec	10 (2.7%)	13 (3.6%)
Grade 2: QTc > 470 - 500 msec or deltaQTc > 60 msec	11 (2.9%)	8 (2.2%)
Grade 3/4: QTc > 500 msec	1 (0.3%)	0 (0.0%)
TOTAL	343 (91.5%)	313 (86.9%)

(Reproduced from Sponsor, Table 13.9.2, page 2947, Study A6181034 Study Report)

6.3 Thorough QTc Study (Study A6181005)

6.3.1 Title

A phase 1 study to evaluate the effect of SU011248 on QTc interval in subjects with advanced solid tumors.

6.3.2 Protocol Number: A6181005

6.3.3 Objectives

Primary:

- To assess the effects of high peak plasma concentrations of SU011248 + SU012662 on the QTc interval in patients with advanced refractory solid tumors.

Secondary:

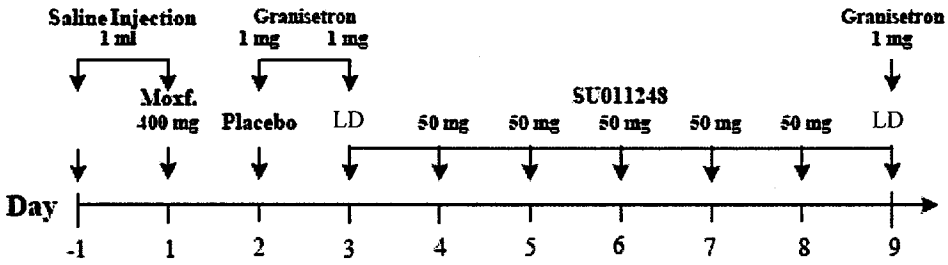
- To evaluate the safety and tolerability of SU011248 after administration of a total of 2 loading doses and maintenance doses over 5 days.
- To evaluate the concentration-effect relationship between the QT and QTc interval and pharmacokinetic (PK) parameters of SU011248 and SU012662.

6.3.4 Design

6.3.4.1 Description

This study was a single-blind study in patients with advanced solid tumors. Patients underwent serial electrocardiogram (ECG) assessments on Day -1, then received a single dose of moxifloxacin on Day 1 and a single dose of placebo on Day 2, followed by a 1-week course of SU011248 (loading dose (LD) on Days 3 and 9, maintenance dose on Days 4-8). In order to minimize the probability of inducing nausea and or vomiting, all subjects were pretreated with intravenous granisetron (1 mg) prior to dosing on Days 3 and 9. Granisetron was also administered to subjects on Day 2 (placebo only day) in order to assess its effect on ECG. The study design is displayed in Figure 2.

Figure 2. Study Design



(Reproduced from Sponsor, Figure S1, page 3)

6.3.4.2 Controls

Study included a positive control (moxifloxacin given on day 1) and a placebo control (day 2).

6.3.4.3 Blinding

Single-blind study.

6.3.4.4 Population

Male and female patients, 18-75 years old, with advanced solid tumors either failing standard therapy or for which no standard acceptable therapy existed.

6.3.4.5 Treatment groups

Two loading dose levels were evaluated in this study. The first group received 150 mg as the loading dose on day 3 and day 9, and the second group received 200 mg loading doses on days 3 and 9. Both groups received 50 mg maintenance doses on days 4, 5, 6, 7 and 8.

6.3.4.6 Justification for dose provided

The loading dose on day 3 was calculated to achieve the target concentration of 75-100 ng/ml. The 50 mg maintenance dose was the recommended daily dose, given to maintain therapeutic concentrations. The loading dose on day 9 was calculated to achieve target concentrations that were 2-fold higher (>180 ng/ml) than the therapeutic levels achieved on day 3. Loading doses of 150 mg and 200 mg were given on days 3 and 9.

The sponsor identified an "evaluable population" of patients who achieved the target level (> 180 ng/ml) on day 9 and had adequate ECG measurements. This population would be more appropriate to study since these patients achieved the target concentration.

6.3.4.7 Instructions with regard to meals

On all study periods (days -1, 1, 2, 3 and 9), standardized meals were consumed at identical times and at least 2 hours before any ECG.

6.3.4.8 Study Schedule and Timing of Samples

Table 4. Highlights of Schedule of Interventions

Study Day	-1	1	2	3	4-8	9
Intervention	Baseline	Moxifloxacin 400 mg	Placebo	Loading dose 150 or 200 mg	Daily dose: 50 mg	Loading dose: 150 or 200 mg
12-Lead ECGs	Record ECGs[#]	Record ECGs[#]	Record ECGs[#]	Record ECGs[#]	Not collected	Record ECGs[#]
PK Samples	Not collected	Not collected	Not collected	Collected[##]	Not collected	Collected[##]
Meal Instructions	Standard[###]	Standard[###]	Standard[###]	Standard[###]	Standard[###]	Standard[###]

[#] predose (x3), 2, 4, 6, 8, 12, 16 and 24 hrs postdose

[##] predose (0 hr), and 3, 4, 7, 9, 12 and 24 hr post-dose. Two additional blood samples collected at 72 and 168 hours post Day 9 dose.

[###] Standardized meals given after dose administration, at 4 hrs and 9 hrs after dosing. Light snack given at 7 and 12 hrs after dosing.

(Derived from Sponsor, Table 1, page 67)

6.3.4.9 Sponsor's justification for sampling schedule

No specific justification was provided for the sampling schedule. The intensive PK sampling was presumably to adequately characterize the PK of sunitinib, and the ECG sampling was to adequately evaluate any effect of sunitinib on QT interval.

6.3.4.10 QT Measurement

All ECGs were recorded in triplicate (3 ECGs performed 2 minutes apart). Data from the independent ECG vendor included: QTcB, QTcF, QT, HR, RR, PR, QRS. A study-specific correction factor was derived from Day -1 measurements of QT and RR at 0, 3, 4, 7, 9 and 12 hour time points (see Section 7.2).

The first protocol amendment (10/25/04) changed the method of ECG measurement from machine-read values to the use of on-screen calipers.

6.3.4.11 Baseline

ECGs were collected on day -1 at the same times as those used on day 1, 2, 3 and 9. Data analysis included time-matched baseline correction using Day -1 data as well as a within-day baseline correction using the pre-dose baseline for each arm of the study.

6.3.4.12 Safety assessments

Adverse events(AEs) were assessed throughout the study. Adverse events were graded according to the NCI-CTC, Version 2 (2003).

6.3.4.13 Vital Signs

Heart rate and blood pressure were recorded at baseline (pre-dose) and after each ECG measurement on days -1, 1, 2, 3 and 9. Thereafter, sitting blood pressure and heart rate were measured after each ECG.

7 SPONSOR'S RESULTS

7.1 Study Subjects

A total of 48 patients were enrolled in the study, with 47 patients receiving at least one dose of the drug on day 3 (Intent-to-treat or ITT population, n=47). The "evaluable" population was defined as the subjects who completed all dosing and all PK and ECG evaluations and whole combined (parent+metabolite) concentrations were above the target level of approximately 200 ng/ml (i.e., > 180 ng/ml) on day 9.

Demographics and other patient characteristics are summarized in Table 5.

Table 5. Summary of Demographic and Baseline Characteristics

Variable	ITT Population (N = 47)	Evaluable Population (N = 24)	Safety Analysis Population (N = 48)
Sex [n (%)]			
Male	25 (53)	9 (38)	25 (52)
Female	22 (47)	15 (62)	23 (48)
Race [n (%)]			
White	41 (87)	19 (79)	42 (88)
Asian	3 (6)	3 (13)	3 (6)
Not Listed	3 (6)	2 (8)	3 (6)
Age (years)			
Mean (std)	59.4 (14.8)	59.7 (13.1)	59.4 (14.6)
Median (range)	60.0 (20.0, 87.0)	61.0 (31.0, 79.0)	60.0 (20.0, 87.0)
< 65 [n (%)]	27 (57)	14 (58)	28 (58)
≥ 65 [n (%)]	20 (43)	10 (42)	20 (42)
Weight (kg)			
Mean (std)	72.9 (16.6)	73.3 (18.4)	72.4 (16.7)
Median (range)	76.7 (41.7, 119.3)	75.1 (41.7, 119.3)	75.1 (41.7, 119.3)
ECOG performance status [n (%)]			
0	13 (28)	6 (25)	13 (27.1)
1	34 (72)	18 (75)	35 (72.9)

(Reproduced from Sponsor, Table 5, page 101)

7.2 STATISTICAL ANALYSIS

This study is designed to test the null hypothesis that the QT/QTc prolongation is at least 10 ms versus the alternative hypothesis that the QT/QTc prolongation is less than 10 ms. The primary endpoint is QTcF interval for Day 9, at each post-dose timepoint, Day 2 adjusted change from within-treatment day pre-dose in QTcF interval for the evaluable population. For a subject to be considered fully evaluable for QT/QTc prolongation assessment, he must complete the prescribed ten-day study regimen and all of the planned PK and ECG assessments up to Day 10.

Additionally, he must achieve a combined drug (SU011248 + SU012662) concentration of approximately 200 ng/mL. QTc measurements at Hour 0 of Day 3 are used as the within treatment day pre-dose baseline for Day 9.

A mixed linear model includes factors accounting for the following sources of variation: baseline, gender, and treatment.

The sponsor states that "to exclude a 10 ms QT/QTc prolongation for this study, if the upper bounds of the 95% one-sided (90% two-sided) confidence limits for study drug minus placebo are below 15 ms".

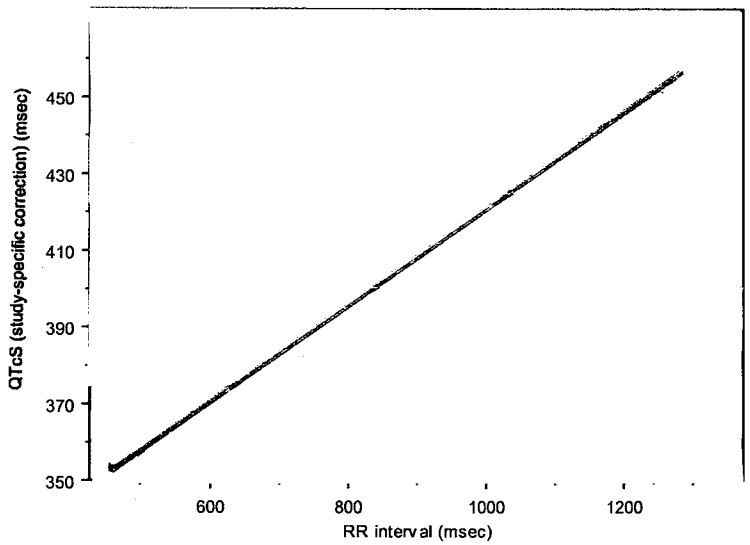
Forty-eight patients with advanced solid tumors were to be enrolled. The sample size for the evaluable population is 24.

7.2.1 QT Interval Correction

Two methods of heart-rate correction were performed: (1) using the Fridericia correction factor, and (2) using a study-specific heart rate correction factor, S, using the data from the baseline session, to calculate a corrected QT interval (QTcS). The data from the placebo session was fit to the equation $\ln QT = \text{Intercept} + S \cdot \ln RR + \text{error}$, where S is the slope of the regression line. The estimate of S was used to derive the QTcS interval.

Figure 3 shows the scatter plot of QTcS and QTcF vs. RR interval for the baseline (day -1) data. The plots suggest that the study-specific correction factor adequately corrects for the relationship between QT and RR

Figure 3. FDA Analysis: Scatter Plot of QTcS (Study-Specific Correction) vs. RR Interval (upper panel) and QTcF (Fridericia Correction) vs. RR Interval (lower panel) for Baseline (day -1) Data (ITT population)



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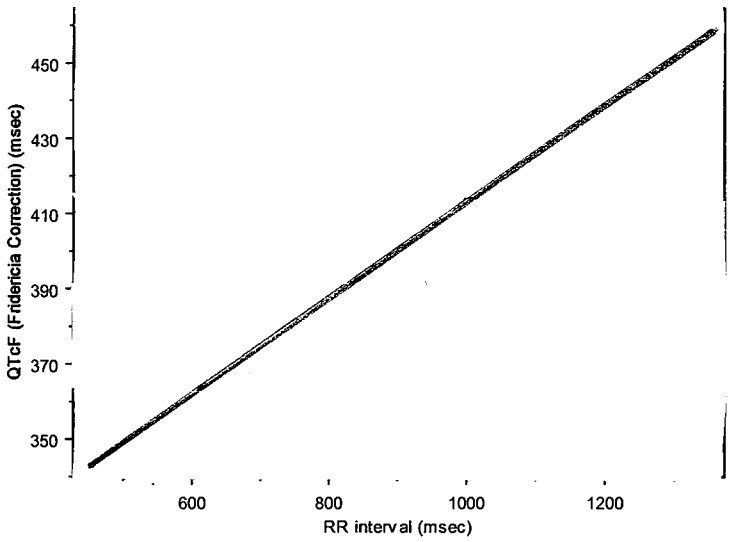

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7.2.2 Sensitivity Analysis

The moxifloxacin arm of the study was used as an active control to establish that the study design had adequate sensitivity to detect a significant change in QTc. Table 6 presents the maximum mean placebo-adjusted QTc changes from baseline observed after treatment with moxifloxacin (evaluable and ITT populations, using both baseline correction methods). As Table 6 shows, the maximum mean change obtained was > 5 msec with the 90% CI lower limit > 0, regardless of the population used.

Table 6. Summary of Maximum Mean Placebo-Adjusted Changes from Baseline in QTcF and QTcS Following a Single Dose of 400 mg Moxifloxacin (Evaluable and ITT Populations)

Parameter	Population	Baseline Correction Method	N	Time (hr)	Maximum Mean Placebo-Adjusted Change from Baseline [a]	90% CI [a]
QTcF (msec)	Evaluable	Within-day	24	24	9.8	4.7, 14.9
QTcF (msec)	Evaluable	Time-matched	24	24	5.6	1.9, 9.3
QTcF (msec)	ITT	Within-day	46	4	9.0	5.3, 12.6
QTcF (msec)	ITT	Time-matched	47	24	5.5	3.4, 7.7
QTcS (msec)	Evaluable	Within-day	24	24	10.0	5.0, 15.0
QTcS (msec)	Evaluable	Time-matched	24	24	5.7	2.0, 9.4

[a] Means and 90% confidence intervals (CI) were computed from change from baseline data using ANCOVA models with terms of baseline, gender, and treatment.

(Reproduced from Sponsor, Table 10, page 111)

7.2.3 Primary Analysis

Changes in QTc on day 2, following granisetron, are tabulated in Table 7. Granisetron had a negligible effect on the QTc, with the maximum mean change in QTc of ≤ 2 msec. It should be noted that the mean maximal values for granisetron were time-matched for baseline period (which is equivalent to a placebo for the granisetron) and represent a delta QTC.

Table 7. Summary of Maximum Mean Change from Baseline in QTcF and QTcS Following a Single Dose of 1 mg Granisetron (Evaluable and IT Populations)

Parameter	Population	Baseline Correction Method	N	Time (hr)	Maximum Mean Placebo-Adjusted Change from Baseline *	90% CI *
QTcF (msec)	Evaluable	Within-day	24	4	0.8	-3.9, 5.5
QTcF (msec)	Evaluable	Time-matched	24	4	1.5	-1.6, 4.5
QTcF (msec)	ITT	Within-day	47	7	0.1	-2.9, 3.1
QTcF (msec)	ITT	Time-matched	44	4	2.0 **	-0.1, 4.2
QTcS (msec)	Evaluable	Within-day	24	4	0.6	-4.2, 5.3
QTcS (msec)	Evaluable	Time-matched	24	4	1.3	-1.7, 4.3

* Means and 90% confidence intervals (CI) were computed from change from baseline data using ANCOVA models with terms of baseline, gender, and treatment.
** Data shown are the maximum values obtained post-dose.

(Reproduced from Sponsor, Table 11, page 113)

Figure 4 shows the time course of placebo-adjusted QTcF changes from baseline following the day 3 and day 9 doses of sunitinib.

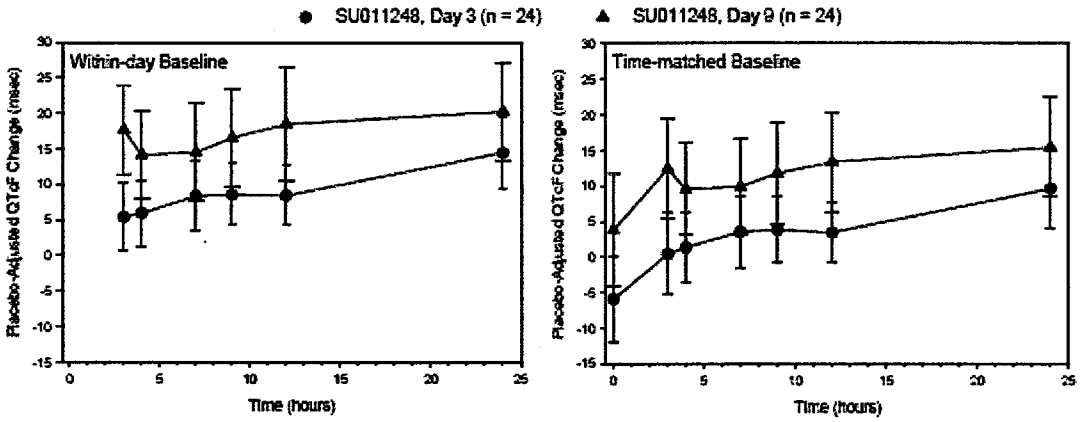
Table 8 displays a summary of the results for maximum mean changes from baseline in QTc following sunitinib on day 3 and day 9.

An effect on QTc (defined as a mean placebo-adjusted change of ≥ 10 msec with a 90% CI upper limit ≥ 15 msec) was observed on Day 3 using the within-day baseline correction method, and on Day 9 using both baseline correction methods (see table above). The maximum mean placebo-adjusted change from (time-matched) baseline QTcF was 14.5 msec (90% CI: 9.5 – 19.5) at therapeutic levels of sunitinib (day 3) and was 20.3 msec (90% CI: 13.4 – 27.1) at supratherapeutic (2-fold higher than therapeutic) levels of sunitinib.

The method of baseline correction did not markedly affect the shape of the QTc change versus time curves, though the magnitude of change was lower for the time-matched baseline correction method compared to the within-day correction (Figure 4).

The maximum mean changes in QTc occurred at the 24 hr time-point on both day 3 and day 9. Visual examination of the time course of QTc changes suggests a delay in the time of the peak effect relative to peak concentrations (Tmax ranged from 7 to 10 hrs).

Figure 4. Plot of Mean (90% CI) Placebo-Adjusted QTcF Changes from Baseline vs. Time for All Patients Combined (Evaluable Population)



(Reproduced from Sponsor, Figure 4, page 114)

Table 8. Summary of Maximum Mean Placebo-Adjusted Changes from Baseline in QTcF and QTcS Following Dosing with Sunitinib – Day 3 and Day 9 – All Patients Combined (Evaluable and IT Populations).

Parameter	Population	Baseline Correction Method	N	Time (hr)	Maximum Mean Placebo-Adjusted Change from Baseline *	90% CI *
Day 3						
QTcF (msec)	Evaluable	Within-day	24	24	14.5	9.5, 19.5
QTcF (msec)	Evaluable	Time-matched	24	24	9.6	4.1, 15.1
QTcF (msec)	ITT	Within-day	47	24	11.9	8.6, 15.2
QTcF (msec)	ITT	Time-matched	47	24	6.9	3.3, 10.4
QTcS (msec)	Evaluable	Within-day	24	24	12.7	8.1, 17.3
QTcS (msec)	Evaluable	Time-matched	24	24	7.4	2.4, 12.5
Day 9						
QTcF (msec)	Evaluable	Within-day	24	24	20.3	13.4, 27.1
QTcF (msec)	Evaluable	Time-matched	24	24	15.4	8.4, 22.4
QTcF (msec)	ITT	Within-day	43	24	17.7	12.9, 22.6
QTcF (msec)	ITT	Time-matched	43	24	12.7	8.1, 17.3
QTcS (msec)	Evaluable	Within-day	24	24	19.2	12.3, 26.1
QTcS (msec)	Evaluable	Time-matched	24	24	13.9	7.0, 20.9

(Reproduced from Sponsor, Table 12, page 115)

7.2.4 Categorical Analysis

Table 9 and Table 10 display the number (and percent) of patients with QTc elevations (absolute values and change from baseline) following treatment with moxifloxacin, placebo (granisetron), and sunitinib. There were 4 evaluable patients (all female) who showed QTc intervals > 450 msec and 6 ITT patients (5 female) who showed elevations in QTc > 450 msec. Changes in QTc (time-matched) between 30 and 60 msec occurred in 9 evaluable patients and changes in QTc > 60 msec was seen in 1 evaluable patient.

Table 9. Number (%) of patients with QTcF and QTcS Elevations (Absolute Values) Following Treatment with Moxifloxacin, Granisetron and Sunitinib (SU011248) (Evaluable and ITT populations).

			QTc > 450 but ≤ 480 msec			QTc > 480 but ≤ 500 msec [b]		
Parameter	Population	Treatment [a]	Males	Females	All	Males	Females	All
QTcF	Evaluable	Moxifloxacin	0	2 (13.3)	2 (8.3)	0	0	0
		Granisetron	0	0	0	0	0	0
		SU011248	0	3 (20.0)	3 (12.5)	0	1 (6.7)	1 (4.2)
QTcF	ITT	Moxifloxacin	1 (4.0)	3 (13.6)	4 (8.5)	0	0	0
		Granisetron	1 (4.0)	0	1 (2.1)	0	0	0
		SU011248	0	3 (13.6)	3 (6.4)	1 (4.0)	2 (9.1)	3 (6.4)
QTcS	Evaluable	Moxifloxacin	1 (11.1)	2 (13.3)	3 (12.5)	0	0	0
		Granisetron	0	0	0	0	0	0
		SU011248	0	3 (20.0)	3 (12.5)	0	1 (6.7)	1 (4.2)

Note: There were 9 males and 15 females in the evaluable population (total = 24), and 25 males and 22 females in the ITT population (total = 47).

a Data presented for SU011248 are over the entire SU011248 treatment period (Day 3 to Day 9).

b No patients had QTc values > 500 msec.

(Reproduced from Sponsor, Table 13, page 116)

Table 10. Number (%) of Patients with QTcF and QTcS Elevations (Changes from Baseline) Following Treatment with Moxifloxacin, Granisetron and Sunitinib (SU011248) (Evaluable and ITT populations).

			Within-Day Baseline		Time-Matched Baseline	
Parameter	Population	Treatment [a]	Change > 30 but ≤ 60 msec	Change > 60 msec	Change > 30 but ≤ 60 msec	Change > 60 msec
QTcF	Evaluable	Moxifloxacin	2 (8.3)	0	2 (8.3)	0
		Granisetron	0	0	1 (4.2) [b]	0
		SU011248	8 (33.3)	0	9 (37.5)	1 (4.2)
QTcF	ITT	Moxifloxacin	2 (4.3)	0	6 (12.8)	0
		Granisetron	0	0	3 (6.4) [b]	0
		SU011248	11 (23.4)	1 (2.1)	11 (23.4)	2 (4.3)
QTcS	Evaluable	Moxifloxacin	1 (4.2)	0	2 (8.3)	0
		Granisetron	0	0	1 (4.2) [b]	0
		SU011248	6 (25.0)	0	8 (33.3)	0

Note: There were 24 patients in the evaluable population and 47 patients in the ITT population.

a Data presented for SU011248 are over the entire SU011248 treatment period (Day 3 to Day 9).

b All occurrences in the evaluable population and some occurrences in the ITT population were prior to granisetron dosing (i.e., at pre-dose).

(Reproduced from Sponsor, Table 14, page 117)

7.3 Clinical Pharmacology

7.3.1 Phamacokinetic Analysis

There were two loading dose groups included in the evaluable population, 150 mg (n=4) and 200 mg (n=20). Table 11 displays the PK data obtained in the patients in the study. The average Cmax values on day 9 for both loading dose groups exceeded 200 ng/ml, indicating that supratherapeutic (approximately 2-fold) levels were achieved on day 9 in the sample.

Table 11. Summary of Sunitinib (SU011248), Metabolite (SU012662) and Total Drug (Sunitinib+SU012662) PK Parameters by Loading Dose and Study Day (Evaluable Population).

Pharmacokinetic Parameters	Arithmetic Mean (CV %) [Median]			
	Loading Dose 150 mg (N = 4)		Loading Dose 200 mg (N = 20)	
	Day 3	Day 9	Day 3	Day 9
SU011248				
C_{max} (ng/mL)	91.0 (32) [82.7]	169 (32) [165]	137 (23) [127]	208 (26) [195]
T_{max} (hr) *	9.1 (7.5, 23.1)	10.6 (4.2, 12.4)	7.2 (3.3, 12.2)	7.4 (3.4, 11.9)
AUC_{0-24} (ng*hr/mL)	1650 (30) [1559]	3201 (33) [3367]	2255 (20) [2174]	3876 (28) [3601]
C_{trough} (ng/mL)	69.1 (41) [70.2]	133 (37) [144]	85.7 (27) [85.9]	148 (38) [135]
C_{max} Ratio (Day 9/Day 3)	NA	1.85 (10) [1.89]	NA	1.55 (20) [1.50]
AUC_{0-24} Ratio (Day 9/Day 3)	NA	1.93 (16) [1.99]	NA	1.72 (17) [1.75]
SU012662				
C_{max} (ng/mL)	30.9 (47) [32.6]	78.7 (33) [83.4]	28.3 (28) [30.7]	64.9 (37) [58.5]
T_{max} (hr) *	10.5 (7.5, 23.1)	10.6 (2.8, 23.8)	7.2 (3.3, 23.7)	7.4 (3.0, 24.1)
AUC_{0-24} (ng*hr/mL)	578 (53) [574]	1519 (30) [1553]	483 (28) [465]	1220 (36) [1140]
C_{trough} (ng/mL)	26.2 (43) [27.7]	69.6 (33) [74.9]	20.1 (36) [19.3]	49.6 (49) [41.6]
C_{max} Ratio (Day 9/Day 3)	NA	2.75 (23) [2.80]	NA	2.36 (30) [2.25]
AUC_{0-24} Ratio (Day 9/Day 3)	NA	2.98 (33) [2.96]	NA	2.57 (26) [2.49]
Total Drug				
C_{max} (ng/mL)	122 (30) [118]	243 (24) [239]	164 (22) [160]	271 (26) [262]
T_{max} (hr) *	10.5 (7.5, 23.1)	10.6 (4.2, 23.8)	7.2 (3.3, 12.2)	7.4 (3.1, 22.3)
AUC_{0-24} (ng*hr/mL)	2229 (27) [2178]	4720 (22) [4678]	2737 (20) [2669]	5096 (29) [5022]
C_{trough} (ng/mL)	95.3 (31) [98.3]	203 (26) [197]	106 (28) [108]	197 (40) [186]
C_{max} Ratio (Day 9/Day 3)	NA	2.03 (8) [2.03]	NA	1.67 (19) [1.70]
AUC_{0-24} Ratio (Day 9/Day 3)	NA	2.16 (16) [2.18]	NA	1.86 (16) [1.86]

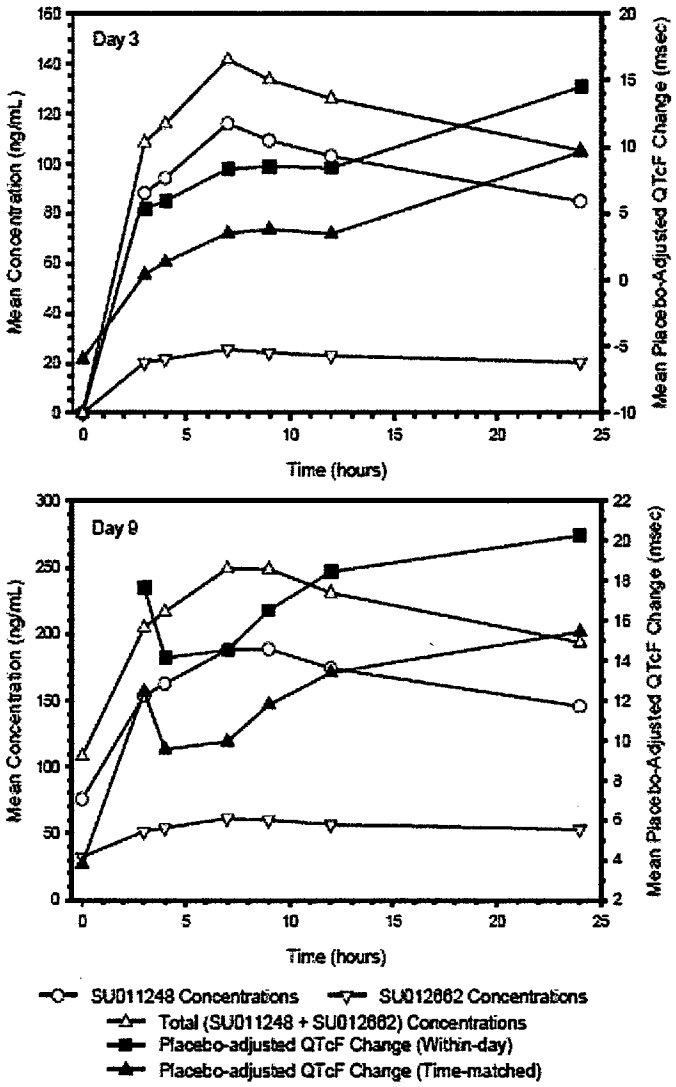
N/A – not applicable.
* Median (min, max).

(Reproduced from Sponsor, Table 9, page 107)

7.3.2 Exposure-Response Relationships

Figure 5 shows an overlay of the time courses of mean concentrations (for sunitinib, metabolite and combined drug) and mean placebo-adjusted QTcF change from baseline on day 3 and day 9. As the plots indicate, there was a delay in the QTcF change relative to the concentrations. Peak changes in QTcF occurred at 24 hrs while peak concentrations were achieved between 7 and 10 hrs.

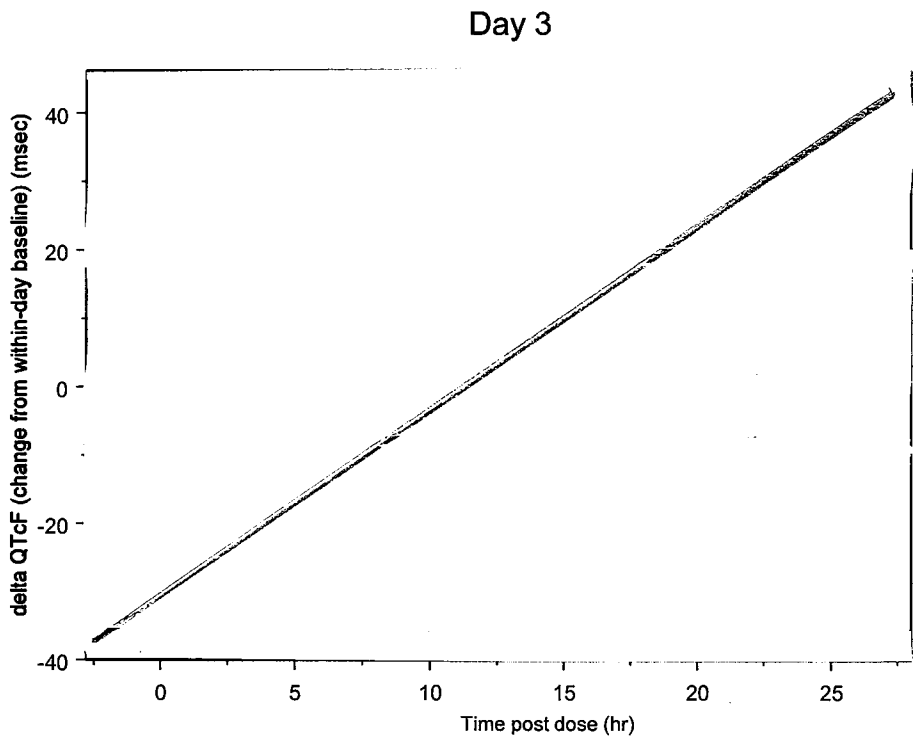
Figure 5. Overlay Plot of Mean Sunitinib, SU012662 and Combined Drug (Sunitinib+SU012662) Concentrations and Mean Placebo-Adjusted QTcF change from Baseline vs. Time for All Sunitinib Loading Dose Groups (Evaluable Population).



(Reproduced from Sponsor, Figure 5, page 121)

The delta QTcF –time profiles for both days 3 and 9 appear to have peaked at the 24 hour time-point and for a few patients, it appeared to be further increasing (see Figure 6 and Figures A6 and A7 in Appendix). For day 9 there were two additional time points where ECG was collected at 72 and 168 hours. For 3 patients on day 9 the QTc appeared to be higher at 72 and 168 hrs. We are unsure if the QTc may have peaked beyond the 24 hour timepoint. Given this observation, we would want to include the most conservative estimates in the label (i.e. the within-day correction on days 3 and 9). Also, the sponsor's pre-specified endpoint for the QTc study was the day 9, placebo corrected, within-day baseline corrected change in QTcF.

Figure 6. FDA Analysis: Individual Delta QTcF vs. Time Plots for All Patients on Day 3 (upper panel) and Day 9 (lower panel)



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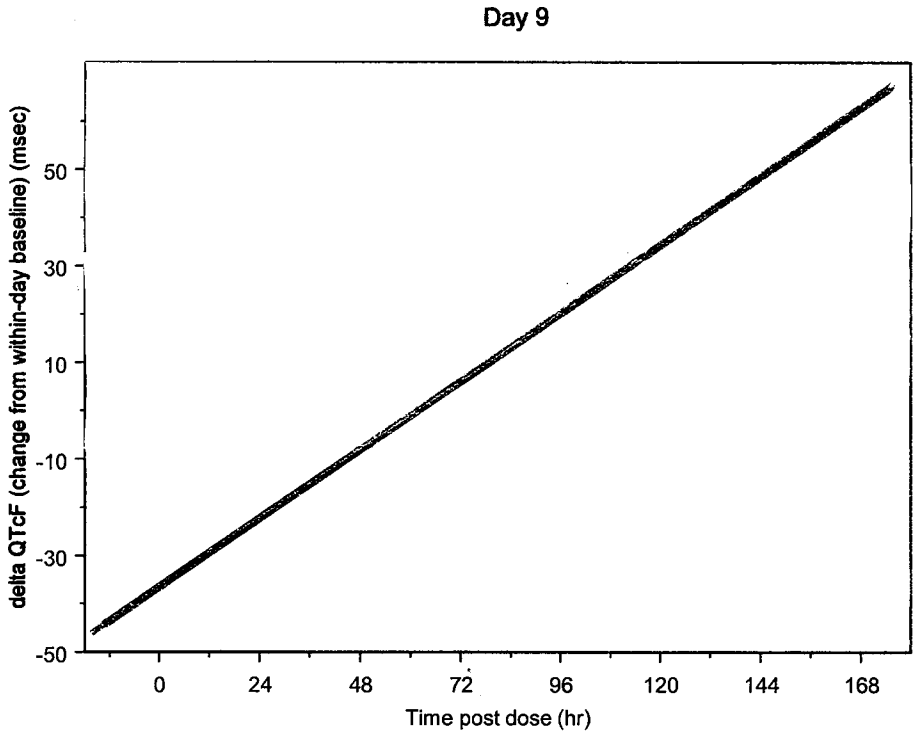
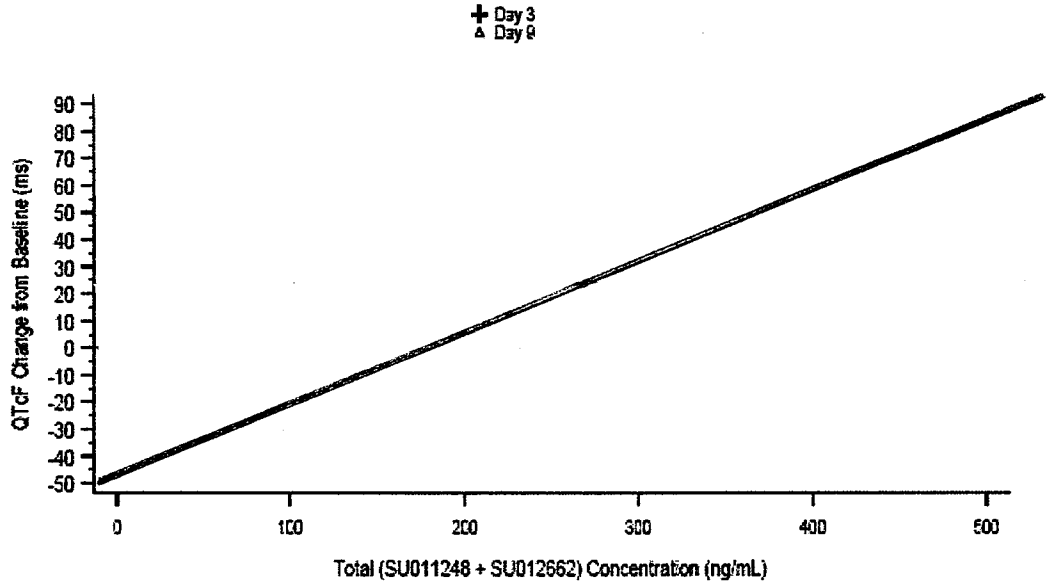


The delay in peak QTc changes relative to concentration indicates a disequilibrium between concentration and effect. This is demonstrated by a counter-clockwise hysteresis in plots of concentration vs. QTc change, as seen in the Appendix (figure A4: day 3 concentrations vs. delta QTcF and figure A5: Day 9 concentrations vs. delta QTcF). This pattern was seen in over 50% of individuals in the study.

Figure 7 shows the scatter plots of placebo-adjusted QTcF change from baseline vs. combined sunitinib+SU012662 concentration. The plots suggest a positive association between change in QTcF and concentration. The sponsor indicated that mixed-effect modeling could not be conducted due to the disequilibrium between concentration and QTcF, which violates the assumption of the linear PK-QT model that was to be utilized for this analysis.

Figure 7. Scatter Plot of Individual Placebo-Adjusted QTcF Changes from Baseline Versus Total Drug (Sunitinib + SU012662) Concentrations (ITT population). Upper panel: Time-Matched Baseline-Correction. Lower panel: Within-day Baseline Correction.



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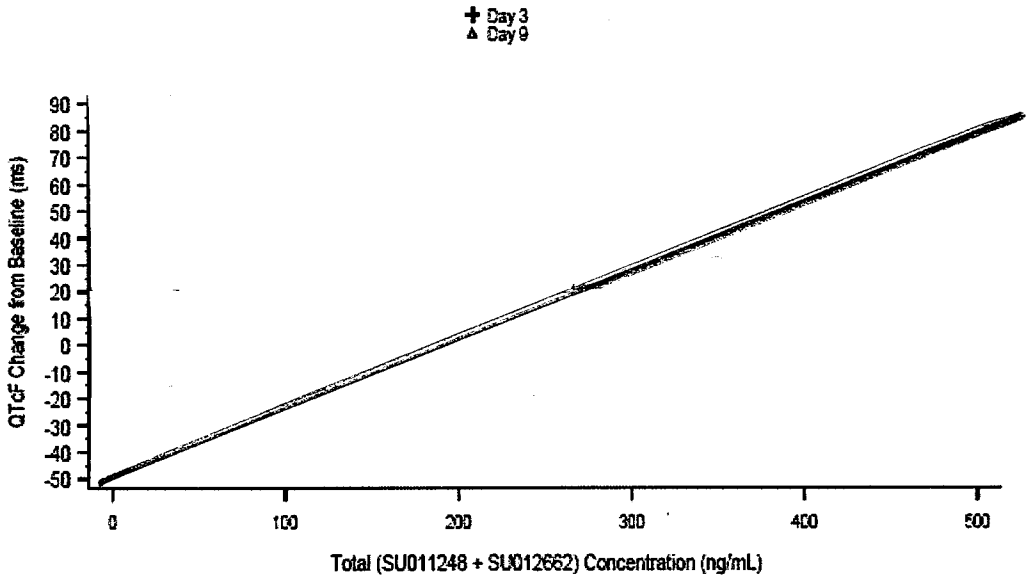

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(Reproduced from Sponsor, Figure 6-7, page 122-123)

8 REVIEWERS' ASSESSMENT

8.1 Evaluation of Study Design

- **Adequacy of Exposure:** The effect of sunitinib on QT intervals was evaluated at therapeutic levels (following the loading dose on day 3) and at supratherapeutic levels (approximately 2-fold higher) following the dose on day 9. This range of exposures was adequate.

- **Adequacy of sampling:** Sampling for PK and ECGs on day 3 and 9 was conducted for 24 hrs following dosing. While additional samples were collected at 72 hrs and 168 hrs after the day 9 dose, these time points were not included in the QTc analysis. Given the time delay between concentrations and QTc changes and that most patients showed maximal changes at the 24 hr time point, it would have been helpful to have additional data points beyond 24 hrs for a more complete characterization of the time course of QTc changes.

- **Adequacy of Controls:** The sponsor included a baseline period, a positive control, and a placebo control as part of this study, which was appropriate. However, given the drug had a long half-life and this was a study in patients, the treatments (moxifloxacin, placebo and sunitinib) could not be given in randomized order. Instead, the sponsor fixed the order of the treatments, with moxifloxacin on day 1, placebo on day 2, and sunitinib starting on day 3 (through day 9) of the study. The moxifloxacin maximum mean occurred at 24 hours. The Tmax for moxifloxacin usually ranges from 2-3 hours. In this study, mean profile for the QTcF indicates that there is a peak around 3-4 hours and another peak around 24 hours. After removal of one of the outliers from the dataset, the maximum mean occurred at 3-4 hours, however, the mean profile still indicated that there is a peak occurring at 24 hours. The reason for this is unclear.

- **Baseline correction:** Two methods of baseline correction were performed: time-matched and within-day. One concern with the within-day baseline correction is the potential for a carryover effect since the moxifloxacin treatment was given the day before the placebo treatment. However, given that there was a common baseline period (day -1) for both placebo and sunitinib treatments, a time-matched baseline correction would cancel out when change in QTc for placebo was subtracted from change in QTc for sunitinib. Hence, it would be more appropriate to use the within-day baseline correction instead of the time-matched baseline correction.
- **Heart rate correction factor:** Two methods of heart-rate correction were examined in the sponsor's analysis: Fridericia correction and study-specific correction. The study-specific correction factor was estimated based on the data obtained under baseline conditions; however, examination of the data indicated that the correction factor was affected by the treatment. Since sunitinib caused a reduction in heart-rate, this may have influenced the QT vs. RR relationship and estimate of the heart-rate correction factor from data collected under drug condition. Evaluation of the QTcF data indicated only a shallow trend for a relationship with the RR interval, suggesting that the Fridericia correction was able to account for the QT – RR relationship.

8.2 Reviewer's Analysis

8.2.1 Moxifloxacin Evaluation

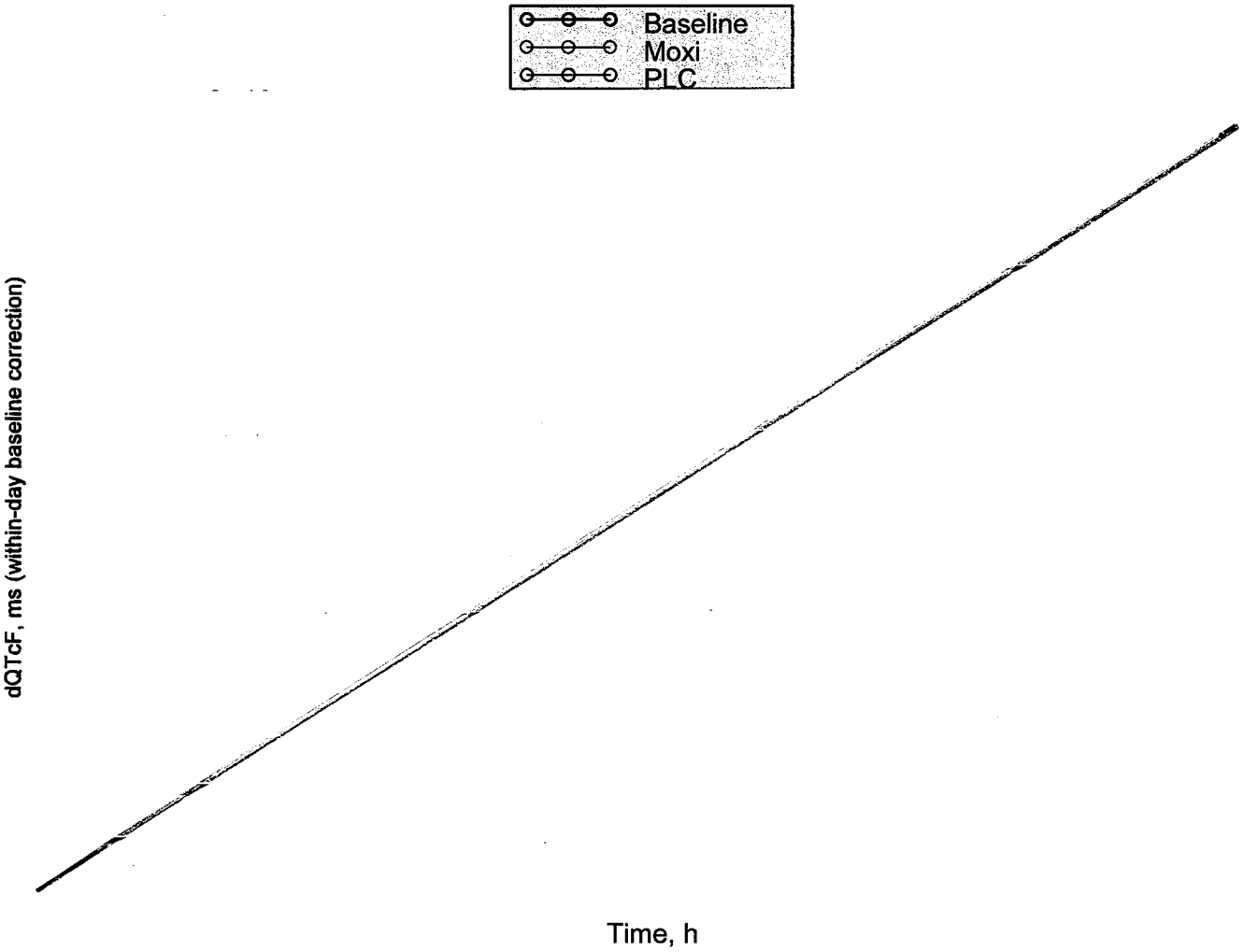
Table 6 indicates that the maximum mean placebo-adjusted change in QTc following moxifloxacin occurs at 24 hrs after the dose. This is different from previously reported Tmax estimates of 2-3 hrs seen for maximal changes in QTc following moxifloxacin.

We wanted to see if the apparent delay in maximum mean effect of moxifloxacin was due to a few patients. Appendix A1 shows the individual profiles of change in QTcF vs. time for each subject for both time-matched baseline corrected QTcF and within-day baseline corrected QTcF. Inspection of individual data suggested that subject 10 was an outlier, showing a large increase in QTcF at 24 hours following moxifloxacin. Also, since this was a fixed order design, where moxifloxacin was followed by placebo, the within-day corrected QTcF from the placebo indicated a maximal decrease at 24 hours.

Exclusion of this subject from the dataset resulted in a lower mean maximal change from baseline at 24 hrs following moxifloxacin. Also now the maximum change now appeared to occur at 3-4 hrs which is closer to the moxifloxacin Tmax (2-3 hours) (Appendix A3).

9 APPENDIX

Appendix A1: Individual change in QTcF vs. time for individual patients for the within-day baseline corrected.



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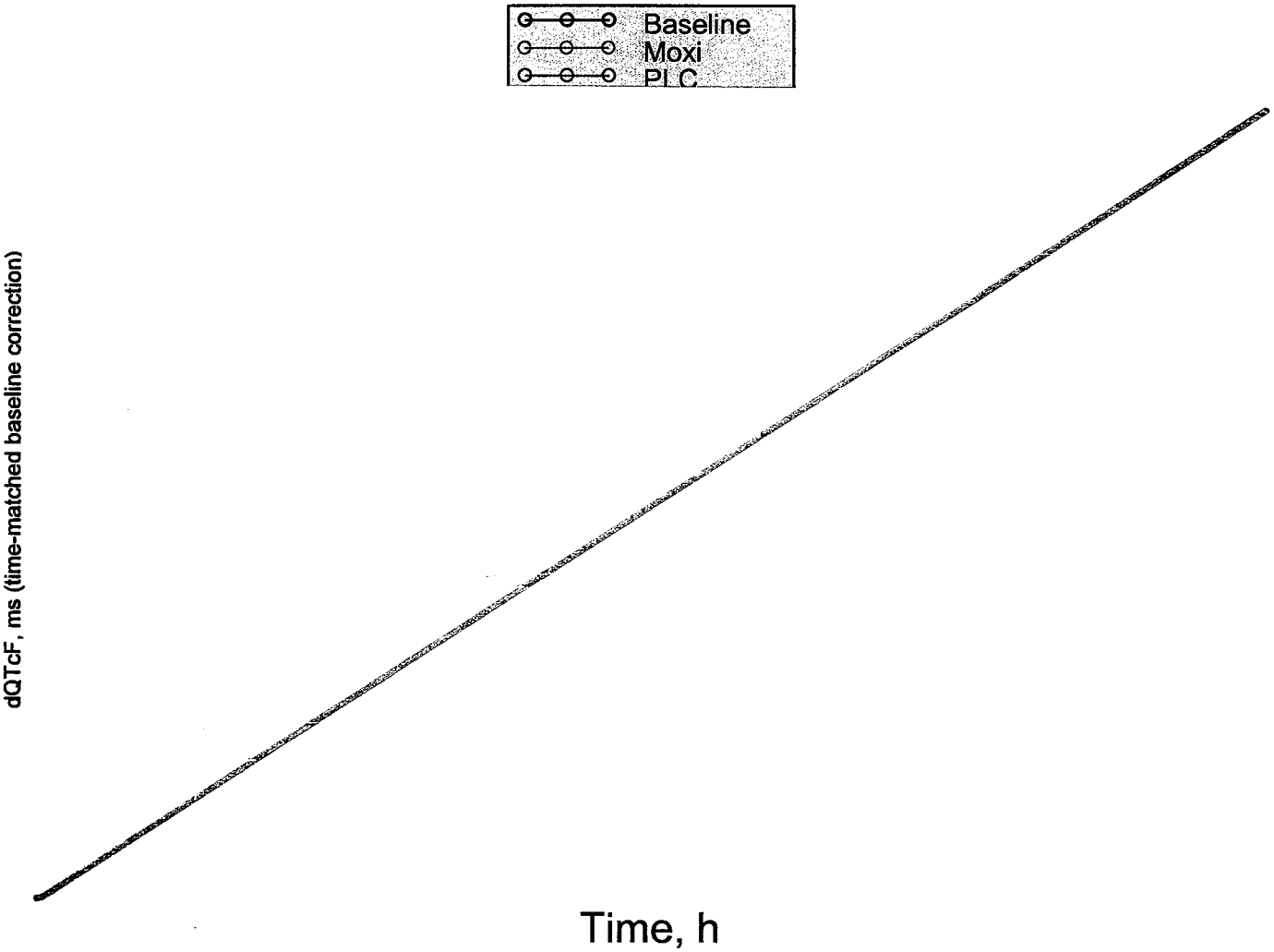
Appendix A2: QTcF vs. time for individual patients using the time-matched baseline correction.



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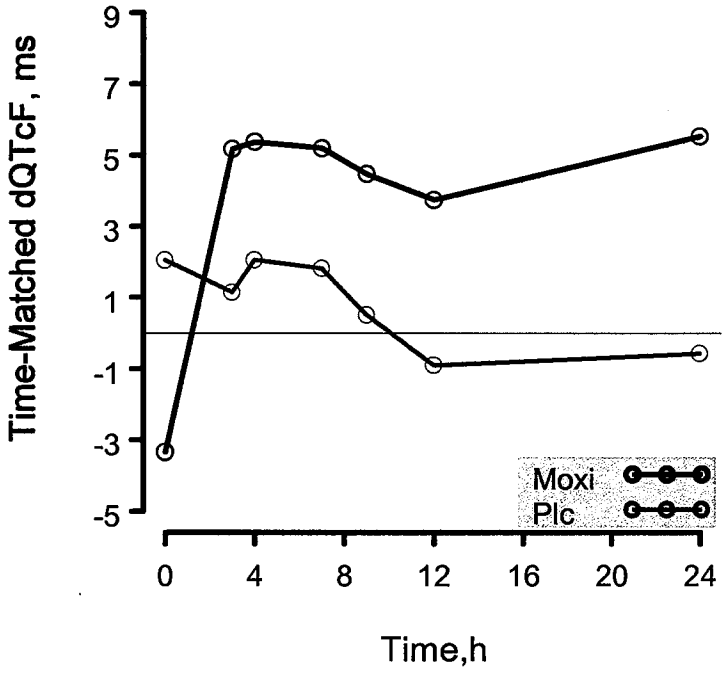
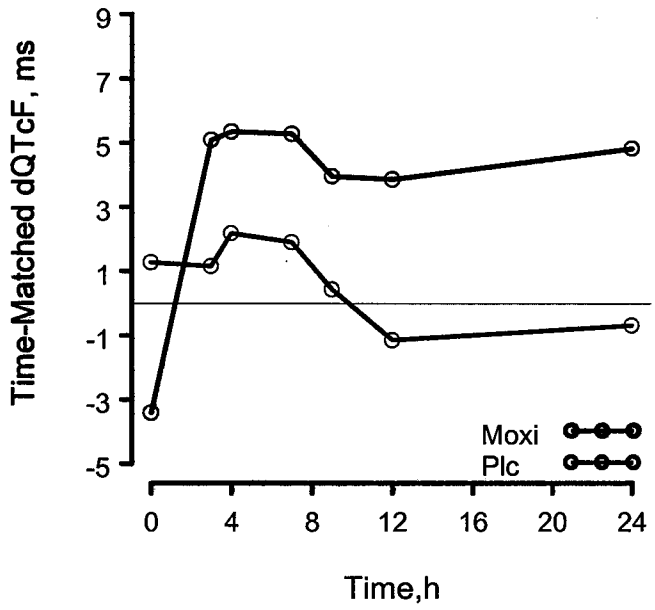
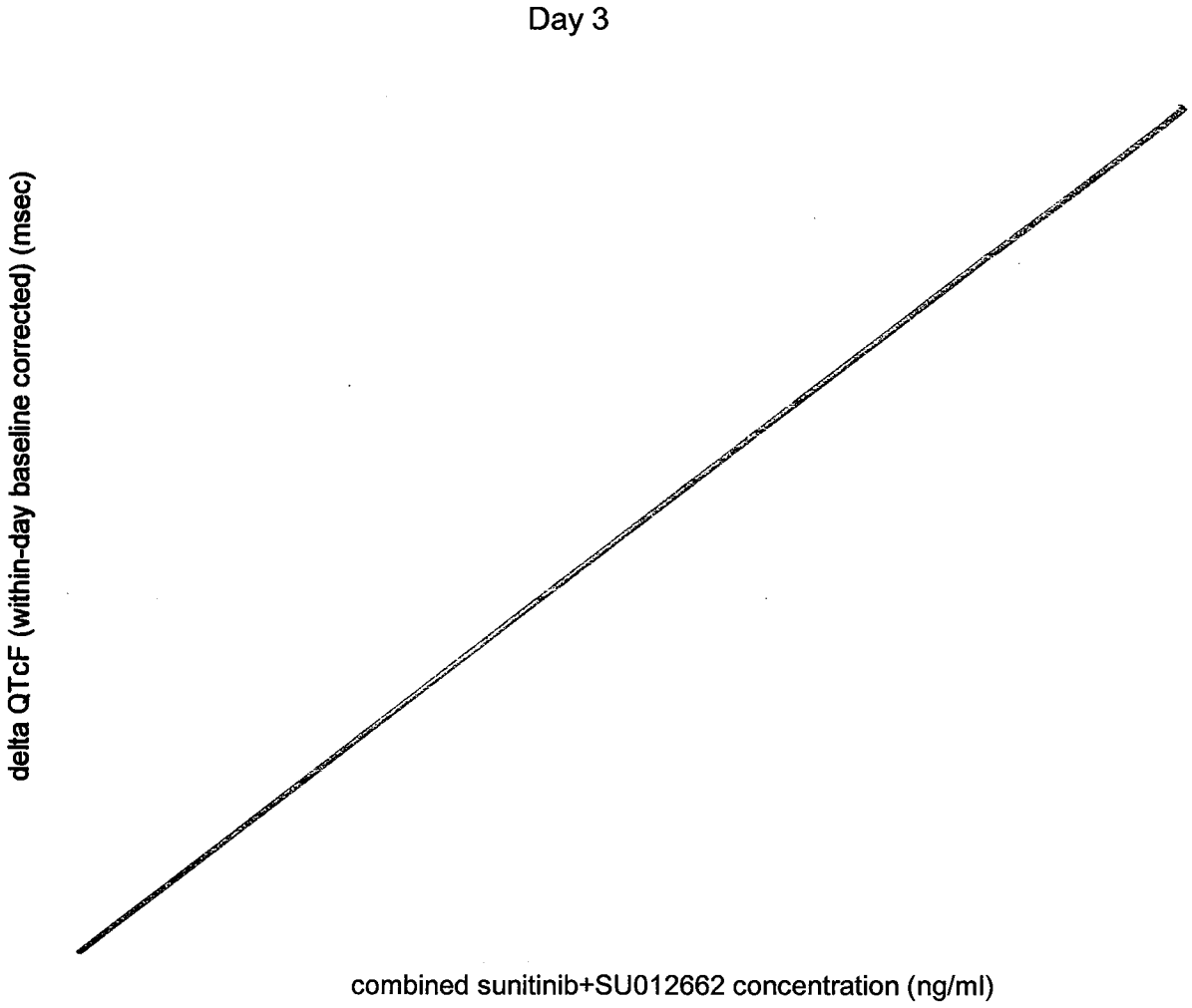
Appendix A3: Mean time-matched QTcF vs. time for moxifloxacin and placebo period. Upper panel shows data across all subjects. Lower panel shows data for all subjects excluding subject number 10.

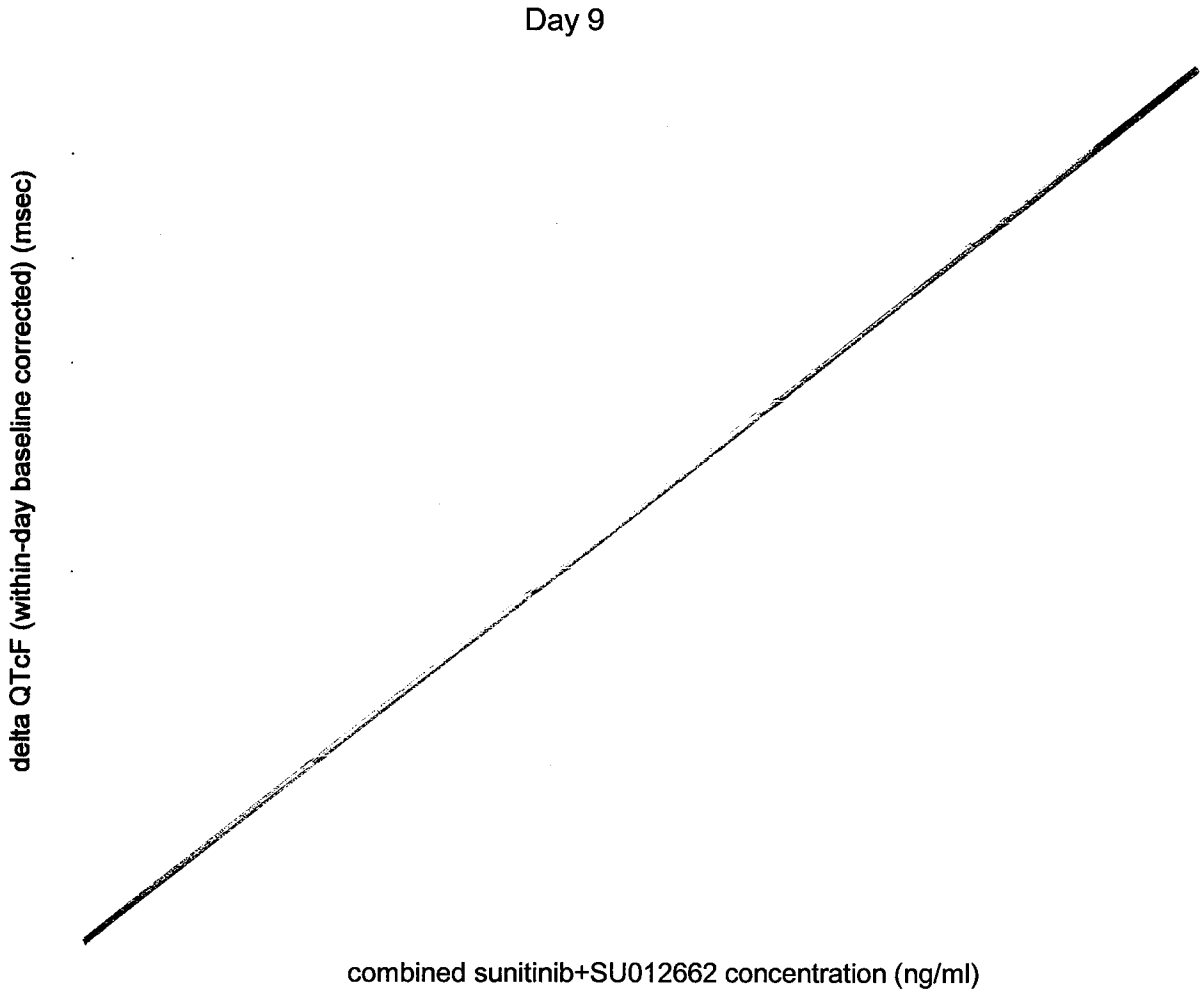




Appendix A4. Delta QTcF (within-day baseline corrected) vs. combined sunitinib + SU012662 concentration, by subject for Day 3.



Appendix A5. Delta QTcF (within-day baseline corrected) vs. combined sunitinib + SU012662 concentration, by subject for Day 9.



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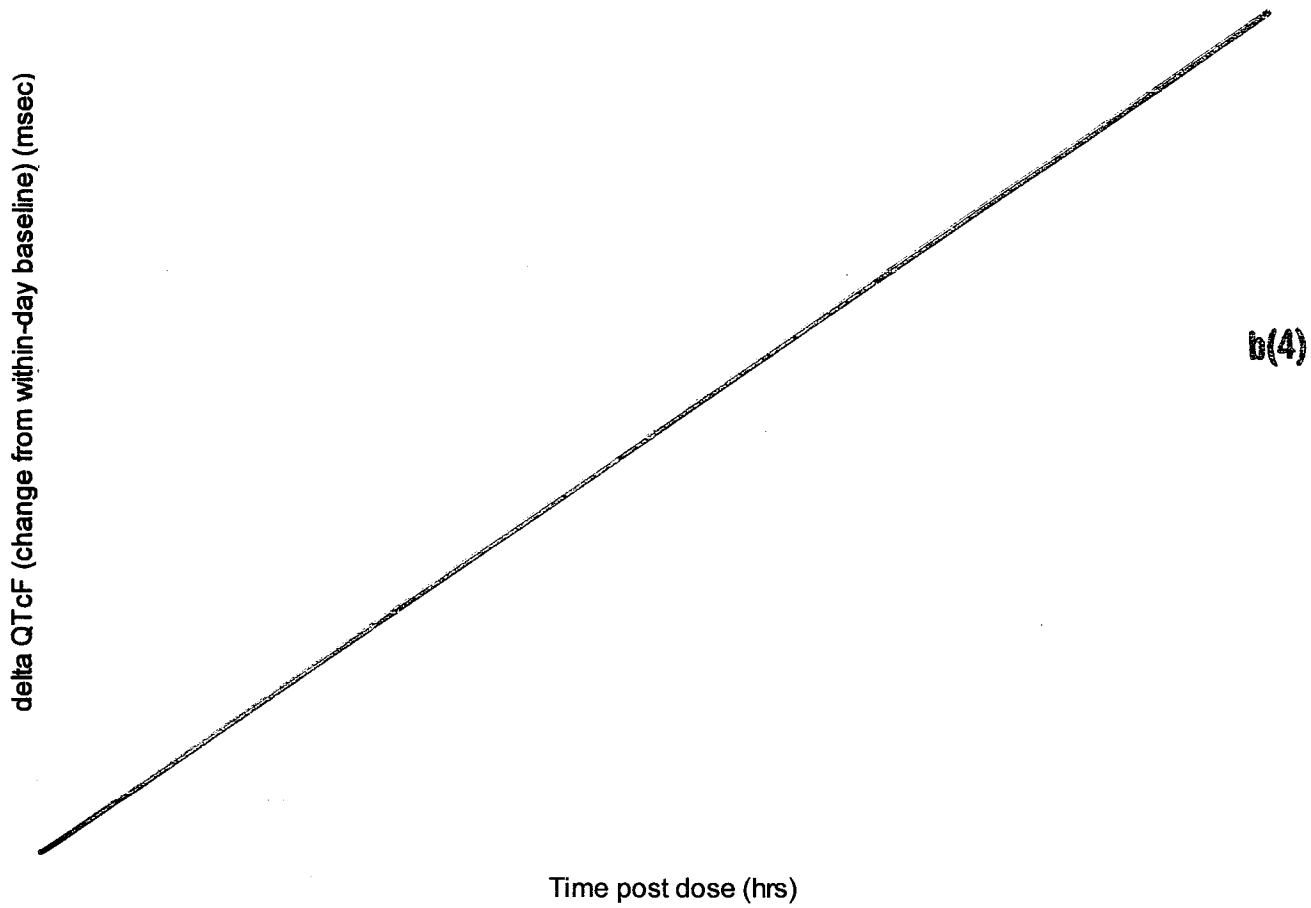
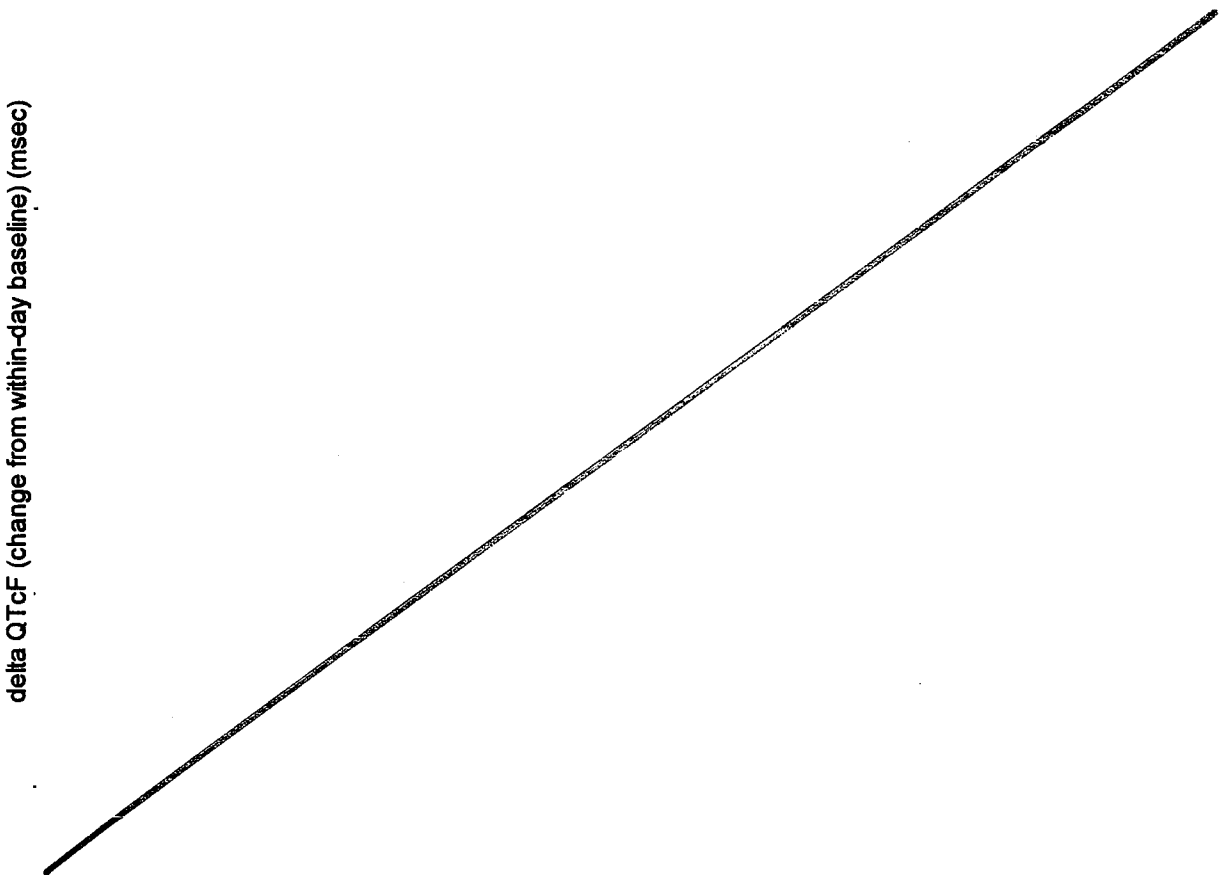
Appendix A6: Individual delta QTcF (change from within-day baseline) vs. time plots following Day 3 loading dose of sunitinib.



Appendix A7: Individual delta QTcF (change from within-day baseline) vs. time plots following Day 9 loading dose of sunitinib.



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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-968
Submission Code	SLR 002, SE8 003, 004 and 006, SE7 005
Letter Date	March 31, 2006/ August 9, 2006
Stamp Date	April 3, 2006/ August 11, 2006
PDUFA Goal Date	February 3, 2007/ February 11, 2007
Reviewer Name	Vicki L. Goodman, M.D.
Review Completion Date	January 25, 2007
Established Name	sunitinib
(Proposed) Trade Name	Sutent®
Therapeutic Class	Receptor Tyrosine Kinase Inhibitor
Applicant	Pfizer
Priority Designation	S (003 and 004)/P (005)
Formulation	oral
Dosing Regimen	50 mg daily
Indication	advanced renal cell carcinoma
Intended Population	same

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Table of Contents

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 conversion of this application for sunitinib for the treatment of advanced renal cell carcinoma (RCC) to regular approval. This recommendation is based on a clinically and statistically robust improvement in progression-free survival in a randomized trial of patients receiving sunitinib as first-line treatment of metastatic renal cell carcinoma (MRCC) compared to those patients receiving interferon-α (IFN- α).

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

The subpart H phase 4 commitments confirming clinical benefit have been fulfilled with these supplements. The sponsor has also fulfilled the commitment to provide additional data relating to patients with abnormal left ventricular ejection fraction form study A6181006.

There is one remaining outstanding required phase 4 commitment from the initial NDA approval:

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

FDA, Pfizer and NCI (the sponsor of this ECOG study) have discussed and implemented a sub-study design to further characterize changes in left ventricular ejection fraction in patients receiving sunitinib compared to those receiving placebo. It is anticipated that data from this sub-study will be available in 2011.

Additionally, one prior commitment, to provide efficacy data from study A6181034 has been partially fulfilled. The commitment required data including PFS, ORR, duration of response and

OS to be submitted. While ORR and PFS data have been submitted, duration of response and OS data were not mature. The submission of these data, when mature, will be the subject of an additional PMC.

- The sponsor will submit the complete study report and datasets with the final statistical analysis of overall survival and duration of response for study A6181034.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Sunitinib received accelerated approval for the treatment of advanced renal cell carcinoma on January 26, 2006 based on durable partial responses in two single-arm studies performed in patients with cytokine-refractory renal cell carcinoma. At the time of approval, a confirmatory randomized study comparing progression-free survival in patients receiving sunitinib to patients receiving IFN-α was ongoing (study A6181034). The current submissions provide updated response data from the larger of the two single-arm studies (A6181006), as well as response data and progression-free survival data from interim analyses of study A6181034. The progression-free survival data is intended to serve as confirmation of clinical benefit in patients with advanced renal cell carcinoma.

1.3.2 Efficacy

Study A6181034 is a randomized, open label trial in patients with treatment-naïve metastatic renal cell carcinoma. Seven hundred and fifty patients were randomized 1:1 to receive either sunitinib or IFN-α. Sunitinib was given at a starting dose of 50 mg orally once daily for 4 weeks, followed by a two week rest period (4/2 schedule). IFN-α was given subcutaneously on three nonconsecutive days per week at a starting dose of 3 MU per dose during the first week, 6 MU per dose the second week and 9 MU per dose thereafter.

Three hundred and seventy-five patients were randomized to each arm. The two treatment arms were well balanced for baseline demographic characteristics, including age, gender, and race. Patients were required to have some component of clear cell histology and most (90%) had undergone prior nephrectomy. The median number of sites of disease was two: common sites included lung, lymph nodes, bone and liver.

The primary endpoint was progression-free survival (PFS), defined as the time from randomization to documented progression or death. Patients who had not progressed or died were censored on the day following the date of the last on study, which included a 28 day

follow-up period after dosing was discontinued. For the primary analysis of PFS in the intent-to-treat (ITT) population based on independent review data, there were 96 events (25.6%) of progression or death on the sunitinib arm compared with 154 events (41.1%) of progression or death on the IFN arm. Median PFS was 47.3 weeks (95% CI 42.6, 50.7) for sunitinib-treated patients and 22.0 weeks (95% CI 16.4, 24.0) for patients treated with IFN; the hazard ratio was 0.415 (95% CI .320, 0.539, p<0.000001). These results were supported by three sensitivity analyses of PFS. Overall survival data were not mature at the time of this analysis.

Overall response rate was higher on the sunitinib arm compared to the IFN arm, with an ORR of 27.5% (95% CI 23.0%, 32.3%) vs. 5.3% (95% CI 3.3%, 8.1%). The response rate noted on the sunitinib arm is similar to the response rates seen in two single-arm trials of sunitinib in patients with cytokine-refractory MRCC.

The updated response data from study A6181006 include an ORR (all partial responses) of 34% (95% CI 25.0, 43.8) as evaluated by the core radiology laboratory, which was the protocol-specified primary analysis. Duration of response data are not mature (the median has not been reached with nine failures and 27 censored patients); the lower bound of the 95% CI was reported as 42 weeks.

1.3.3 Safety

Common drug-related adverse events included GI events [diarrhea (58% sunitinib vs. 20% IFN-α), nausea (49% vs. 38%), mucositis (43% vs. 4%), vomiting (28% vs. 14%), dyspepsia (28% vs. 4%), abdominal pain (22% vs. 12%), gastroesophageal reflux (11% vs. 1%), oral pain (10% vs. 1%), glossodynia (10% vs. 1%) and flatulence (10% vs. 2%)], bleeding (30% vs. 8%), hypertension (30% vs. 4%), dermatologic events [rash (27% vs. 11%), skin discoloration (19% vs. 0%), dry skin (18% vs. 6%), and hair color changes (15% vs. <1%)], palmar-plantar erythrodysesthesia (21% vs. 1%), limb pain (17% vs. 8%), decreases in cardiac ejection fraction (12% vs. 5%), and peripheral edema (11% vs. 4%). Although the incidence of fatigue is not higher in patients treated with sunitinib, the similarity in incidence of fatigue to patients treated with IFN (58% vs. 55%), a well known cause of fatigue, makes it likely that fatigue is also related to sunitinib.

Grade 3/4 adverse events more common on the sunitinib arm included hypertension (10% vs. <1%), diarrhea (6% vs. 0%), palmar-plantar erythrodysesthesia (5% vs. 0%), nausea (4% vs. 1%), vomiting (4% vs. 1%), mucositis (3% vs. 1%), and bleeding (3% vs. 1%).

Less common adverse events that are likely drug related include pharyngeolaryngeal pain (9% vs. 2%), paresthesias (8% vs. 1%), erythema (8% vs. 1%), hemorrhoids (7% vs. 1%), facial edema (7% vs. 1%), nasopharyngitis (7% vs. 1%), skin exfoliation (7% vs. 1%), neuropathy (6% vs. 3%), pleural effusion (5% vs. 1%), lacrimation increased (5% vs. 0%), dysphonia (5% vs. 1%), chromaturia (4% vs. <1%), dysphagia (4% vs. 1%), and hypothyroidism (3% vs. <1%).

Patients receiving sunitinib were more likely to develop significant changes in LVEF and/or clinical evidence of ventricular dysfunction. Thirteen patients on sunitinib (4%) and four on IFN-α (1%) experienced declines in LVEF of > 20% from baseline and to below 50%. One patient who received sunitinib was diagnosed with congestive heart failure and three patients were diagnosed with left ventricular dysfunction.

Grade 3/4 laboratory abnormalities which are more common in sunitinib-treated patients include hematologic abnormalities [neutropenia (12% vs. 7%), thrombocytopenia (8% vs. 0%), and leucopenia (5% vs. 2%)], increased lipase (15% vs. 5%), increased amylase (4% vs. 2%), hyponatremia (5% vs. 2%), hyperuricemia (10% vs. 4%) and hyperbilirubinemia (1% vs. 0%).

1.3.4 Dosing Regimen and Administration

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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 ✓ 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 achieve a similar AUC, a dose reduction to 66% (approximately 37.5 mg) was recommended if sunitinib must be co-administered with a strong CYP3A4 inhibitor.

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 achieve a similar AUC, a dose increase to 175% (87.5 mg) should be considered if sunitinib must be co-administered with a CYP3A4 inducer. If the dose is increased, the patient should be monitored carefully for toxicity.

1.3.6 Special Populations

A hepatic impairment study was submitted and reviewed by the clinical pharmacology review team. Patients with mild to moderate hepatic dysfunction were studied and did not have significantly different exposure to sunitinib compared to patients with normal hepatic function.

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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 Indications

Advanced renal cell carcinoma (RCC) is resistant to standard cytotoxic chemotherapies, with typical response rates of ≤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]

Sorafenib (Nexavar®) was approved on December 20, 2005 for the treatment of advanced renal cell carcinoma based on an improvement in progression-free survival (PFS) compared to placebo in a single 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).[5] The response rate in both arms was negligible (2% for sorafenib-treated patients vs. 0% for placebo-treated patients).

2.3 Availability of Proposed Active Ingredient in the United States

Sunitinib was approved by the U.S. FDA for the treatment of advanced renal cell carcinoma on January 26, 2006.

2.4 Important Issues With Pharmacologically Related Products

Several novel safety issues have been reported with inhibitors of VEGFR. These have included hemorrhage, impaired wound healing, bowel perforation, hypertension, cardiac failure and reversible posterior leukoencephalopathy syndrome. The latter may be associated with acute increases in blood pressure and has been described in patients receiving sunitinib, sorafenib and bevacizumab.

2.5 Presubmission Regulatory Activity

The regulatory history prior to the initial approval is described in detail in the clinical review (NDA 21-968).

On January 26, 2006, the FDA took the following actions:

1. Sunitinib was approved for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumor (GIST)
2. Sunitinib received accelerated approval for the treatment of advanced renal cell carcinoma (RCC)

The GIST approval was based on an improvement in time-to progression compared to placebo in a single randomized trial. The accelerated approval in advanced RCC was based on the demonstration of a 26-37% partial response rate in two single arm trials in patients who had previously received either IFN-α or IL-2 for metastatic disease.

Of note, the RCC approval in "advanced RCC" encompasses a broader population than that studied in the two single-arm trials, where all patients had metastatic disease and all had received prior cytokine therapy. The reasoning behind the expanded indication was twofold. First, patients with advanced, unresectable tumors are treated much like those patients with metastatic disease. Second, requiring prior cytokine therapy, with its limited efficacy and severe toxicities, was felt to be unduly onerous.

Under the subpart H (accelerated approval) regulations, the sponsor is required to provide confirmation of clinical benefit. Study A6181034 is intended to provide confirmation of clinical benefit, as measured by an improvement in progression-free survival. Subpart H post-marketing commitments included the following data:

- 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.

This data was submitted with S003 in March 2006.

- 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

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A6181034. This submission will include the final study report as well as raw and derived data sets.

The data from the second interim analysis, which demonstrated an improvement in PFS, was submitted in August 2006 (S005). Overall survival data were not mature at the time of the analysis.

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.

These data were also submitted in the March 2006 supplement (S003).

The sponsor additional committed to provide follow-up data on cardiac safety related to changes in cardiac ejection fraction, and to further evaluate the extent and clinical relevance of cardiac ejection fraction changes in an NCI-sponsored adjuvant placebo-controlled study in RCC (to be performed under IND 74019).

Follow-up LVEF data from patients on study 1006 was provided in the August 2006 submission.

2.6 Other Relevant Background Information

There have been no market withdrawals or other significant issues outside the U.S.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new CMC data were submitted with this supplement.

3.2 Animal Pharmacology/Toxicology

No new pharmacology and toxicology data were submitted with this supplement.

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

- sNDA submission dated March 31, 2006, including the study report and datasets for study A6181034 and the updated datasets for study A6181006
- an amendment to the initial NDA 21968 dated January 5, 2006 containing the updated derived response dataset for study A6181006
- sNDA submission dated August 9, 2006 including the second interim analysis data from study A6181034, which contains the PFS data.

4.2 Tables of Clinical Studies

The efficacy supplements contain data from 2 clinical studies, as described in Table 1.

Table 1--Summary of Clinical Studies

Study ID	Phase	# Patients	Primary Efficacy Endpoint	Comparison Arm	Status
A6181034	3	750	Progression-Free Survival (PFS)	Interferon-α (IFN- α)	Ongoing; interim analyses based on ORR (1st IA) and PFS (2nd IA)
A6181006	2	106	ORR (CR+PR)	N/A	Continued follow-up for response duration

4.3 Review Strategy

The primary sources of data used in this review were the two efficacy supplements (S003 and S005) submitted in March and August 2006 (see Table x). Study A6181034 was reviewed for efficacy endpoints (ORR and PFS) and safety. Updated ORR data from study A6181006 and limited safety data from this single-arm study (included updated LVEF data in a subset of patients) were also reviewed.

4.4 Data Quality and Integrity

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 data base. 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 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 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 data base was updated to reflect the change.

After all data queries were resolved, a data quality control check was performed before the data base was frozen for analysis. Key safety variables were compared between the CRFs and the data base 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 data base. 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 data base.
This clinical study report has been subjected to quality control processes that were reviewed by the sponsor's own independent quality assurance group.

4.5 Compliance with Good Clinical Practices

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with IRB/IEC, informed consent regulations, and International Conference on 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).

DSI inspections were conducted at two of the highest-accruing sites, described in Table 2 below.

Table 2--DSI Inspection Sites for Study A6181034

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Dr. Ronald Mathew Bukowski The Cleveland Clinic Foundation 9500 Euclid Avenue, R35 Cleveland, OH 44195 United States	A6181034	15	Metastatic Renal Cell Carcinoma
Dr. Thomas E. Hutson Texas Oncology, PA 3535 Worth Street Dallas, TX 75246 United States	A6181034	12	Metastatic Renal Cell Carcinoma

Table 3--Inspection Results by Site

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECT DATE	EIR-REC'VD	CLASS.
Ronald M. Burowski, M.D.	Cleveland, OH	USA	Study: A6181034	Nov. 16 – Dec. 4, 2006	December 14, 2006	VAI
Thomas E. Hutson, M.D.	Dallas, TX	USA	Study: A6181034	Nov 7 – 15, 2006	Pending from DAL-DO	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection/Report not completed

The inspection of the Dallas, TX site (PI: Dr. Hutson) found no deviations from regulations and acceptable data quality.

An explanation of the VAI designation was provided by DSI for the Cleveland Clinic site: "CIN-DO's Investigator Kilker reported that in general, the study site followed study protocol procedures and the study records were found to be organized, complete and legible. Comparison of source data with sponsor's data listings with respect to tumor measurements and objective responses by CT scans found no significant differences or deviations. Consents forms were signed prior to subject participation, and serious adverse events were promptly reported to the IRB and to the sponsor."

An FDA 483 was issued containing three observations pertaining to a.) two subjects with baseline bone scans that were not within the 21 day protocol requirement window; b.) two subjects that were continued on therapy following tumor progression which was contrary to

protocol requirements. However, the site provided documentation of permission from the sponsor to continue treatment of these two subjects; and c.) minor deviations concerning test article storage procedure during a 2 month period.

Recommendation: Data from site are acceptable. Preliminary review of the FDA 483 does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data."

Reviewer's note: Data from the two highest-accruing sites appear to be reliable based on the DSI inspections. No issues with data quality or integrity at other clinical sites were identified.

4.6 Financial Disclosures

Per the sponsor's report, — investigators participated on study A6181034.

- — are certified as having no financial arrangement as defined in 21 CFR 54.2
- The sponsor was unable to obtain financial disclosure information on 2 investigators despite due diligence procedures
- — investigators were reported to have financial information to disclose including — investigators who received "significant payments of other sorts" ranging from $50,000 to nearly $209,000; and / investigators who reported significant equity interest (> $50,000)

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Reviewer's note: Approximately 1% of investigators had a significant financial relationship with the sponsor, either in the form of payments received or equity interest. This is unlikely to be a source of bias because (1) the vast majority of investigators reported having no financial interests to disclose, and (2) the primary efficacy analysis was based on a blinded, independent review of the data.

5 CLINICAL PHARMACOLOGY

There are no new pharmacokinetic or pharmacodynamic data, and no new exposure-response relationships have been evaluated.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The submitted study (A6181034) was conducted in patients with metastatic renal cell carcinoma who had not received prior therapy for metastatic disease (treatment naïve). The currently approved indication for sunitinib is for the treatment of advanced renal cell carcinoma, which includes both those patients with metastatic disease as well as those with locally advanced disease (i.e. not amenable to curative resection). Thus, these supplements are not supporting a new indication for sunitinib, but are providing efficacy data in the first-line population.

6.1.1 Methods

The efficacy review focused primarily on the data from the first-line RCC study (A6181034), which compared sunitinib to IFN-α. Efficacy variables examined include ORR and PFS. OS data were not mature at the time of the second interim analysis. Updated ORR data from study A6181006, the single-arm study in cytokine-refractory patients, were also examined.

6.1.2 General Discussion of Endpoints

The primary endpoint of the submitted study is progression-free survival (PFS). The correlation between PFS and OS in RCC is not well established. However, delaying disease progression may itself be considered a clinical benefit if progression results in a worsening of disease symptoms. The April 2005 draft guidance for industry on clinical trial endpoints for the approval of cancer drugs and biologics, states that PFS prolongation might be an acceptable surrogate endpoint for clinical benefit to support full approval. Important considerations include the magnitude of the effect, the toxicity profile of the treatment and the clinical benefits and toxicities of available therapies. For the assessment of PFS, randomized blinded studies with a blinded review are recommended. Because of the route of administration of these two drugs and their toxicity profiles, blinding of patients and investigators was not feasible. However, radiographic data were subjected to blinded review.

PFS has recently been accepted by FDA as an endpoint supportive of regular approval in advanced renal cell carcinoma. On December 20, 2005, the Division of Oncology Drug Products approved sorafenib (Nexavar®) based on an improvement in PFS. 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). A detailed review of the data which support PFS as a surrogate for OS in RCC is available in the clinical review of the sorafenib NDA (NDA 21-923) by Dr. Robert Kane of the Division of Drug Oncology Products.

6.1.3 Study Design

Study A6181034 is an ongoing, randomized, multi-center, international, open-label study comparing sunitinib to IFN-α for the first-line treatment of metastatic renal cell carcinoma (MRCC).

Protocol Landmarks:

Final Protocol	**March 9, 2004**
Amendment #1	**June 2, 2004**

Major changes were:

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- Addition of PFS as a secondary endpoint (TTP was the primary endpoint)
- Change in stratification factors (exclusion of stratification based on Motzer Criteria and inclusion of LDH, ECOG performance status and prior nephrectomy.
- Removal of ACTH stimulation testing
- Change in adverse event reporting requirements to be compliant with European standards
- Patient reported outcomes (PRO) section has been modified to include a new instrument
- (FACT-Advanced Kidney Cancer Symptom Index [FKSI])

First Patient Visit **August 10, 2004**
Amendment #2 **February 25, 2005**

Major changes were:

- The primary endpoint was changed from TTP to PFS, and TTP became a secondary endpoint
- The definitions of the endpoints were revised.
- Changes were made to the eligibility criteria to exclude
  - Patients with hypertension that could not be controlled by medication
  - Patients receiving therapeutic doses of Coumadin.

Data Cutoff for Interim Analysis of Response **July 4, 2005**

Amendment #3 **October 27, 2005**
Major changes were:

- A second interim analysis was added to the protocol.
- Subject withdrawal criteria were modified to state that subjects with evidence of clinical benefit despite RECIST-defined progressive disease were allowed to continue study treatment.

Data Cutoff for Interim Analysis of PFS **November 15, 2005**

Choice of control arm:

Interferon alpha was chosen as the control arm. Although not FDA approved for this indication, IFN-α is a commonly used and accepted treatment in this disease setting. The dose of 9 MU TIW of IFN-α was selected based on considerations of tolerability, safety, and efficacy. A dose of 18 MU TIW was intolerable in more than half of patients receiving IFN-α in a randomized trial comparing IFN-α plus vinblastine versus vinblastine alone. Further, no difference in survival was observed between patients who received 18 MU TIW of IFN-α throughout the study as planned, compared to those patients for whom doses were reduced to 9 MU TIW.[6] The 9 MU TIW dose has been commonly used in clinical practice in many countries because of improved tolerability and has become the standard dose in trials using interferon as the comparator arm.[7]

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Objectives/Endpoints:

The primary objective of the study is to compare the progression-free survival (PFS) of sunitinib versus that of IFN- α for the first-line treatment of patients with MRCC.

Secondary objectives include:

- To compare overall response rate (ORR)
- To compare overall survival (OS)
- To compare time-to-progression (TTP)
- To compare patient reported outcomes
- To evaluate the safety and tolerability of sunitinib
- To assess the cost effectiveness of sunitinib compared to IFN-α in first-line MRCC
- To evaluate exposure-response relationships for both efficacy and safety
- To explore correlations of potential biomarkers with cancer and treatment related outcomes

The primary endpoint was PFS; major secondary endpoints included ORR, OS, TTP and duration of response (DR).

Eligibility Criteria:

Inclusion Criteria:

1. Histologically confirmed renal cell carcinoma with metastases with a component of clear (conventional) cell histology.

2. Evidence of unidimensionally measurable disease (ie, ≥1 malignant tumor mass that can be accurately measured in at least 1 dimension ≥20 mm with conventional computerized tomography [CT] or magnetic resonance imaging [MRI] scan, or ≥10 mm with spiral CT scan [if spiral CT scan is used, minimum lesion size should be twice the reconstruction interval used, e.g., if reconstruction size is 7 mm, lesion size should be ≥14 mm]). Bone lesions, ascites, peritoneal carcinomatosis or miliary lesions, pleural or pericardial effusions, lymphangitis of the skin or lung, cystic lesions, or irradiated lesions are not considered measurable.

3. Male or female, 18 years of age or older.

4. ECOG performance status 0 or 1.

5. Resolution of all acute toxic effects of prior radiotherapy or surgical procedure to NCI CTCAE Version 3.0 grade ≤1.

6. Adequate organ function as defined by the following criteria:
   - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT])

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≤2.5 x central laboratory upper limit of normal (CL-ULN), or AST and ALT ≤5 x CL-ULN if liver function abnormalities are due to underlying malignancy
- Total serum bilirubin ≤1.5 x CL-ULN
- Absolute neutrophil count (ANC) ≥1500/μL
- Platelets ≥100,000/μL
- Hemoglobin ≥9.0 g/dL
- Serum calcium ≤12.0 mg/dL
- Serum creatinine ≤1.5 x CL-ULN
- Prothrombin time (PT) ≤1.5 x CL-ULN
- Left ventricular ejection fraction (LVEF) ≥ lower limit of normal (LLN) as defined by the institution performing the scan as assessed by multigated acquisition (MUGA) scan

7. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.

8. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

Exclusion Criteria:

1. Renal cell carcinoma without any clear (conventional) cell component.

2. Prior systemic (including adjuvant or neoadjuvant) therapy of any kind for RCC (including immunotherapy, chemotherapy, hormonal, or investigational therapy).

3. Major surgery or radiation therapy <4 weeks of starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated.

4. NCI CTCAE grade 3 hemorrhage <4 weeks of starting the study treatment.

5. 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.

6. History of or known brain metastases, spinal cord compression, or carcinomatous meningitis, or evidence of brain or leptomeningeal disease on screening CT or MRI scan.

7. Any of the following within the 12 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism.

8. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.

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9. Ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2, atrial fibrillation of any grade, or prolongation of the QTc interval to >450 msec for males or >470 msec for females.

10. Hypertension that cannot be controlled by medications (>150/100 mm/Hg despite optimal medical therapy).

11. Ongoing treatment with therapeutic doses of Coumadin (low dose Coumadin up to 2 mg PO daily for deep vein thrombosis prophylaxis is allowed).

12. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

13. Current treatment on another clinical trial.

14. Pregnancy or breastfeeding. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.

Randomization and Stratification:

Patients were randomized 1:1 to treatment with either sunitinib or IFN-α and were stratified according to:

1. LDH (> 1.5 versus ≤ 1.5 x the upper limit of normal [uln])
2. ECOG performance status (0 vs. 1)
3. prior nephrectomy (yes vs. no)

Study Medications:

Arm A: sunitinib at a starting dose of 50 mg daily for 4 weeks followed by a 2 week treatment break (the 4/2 schedule)

Arm B: IFN-α given subcutaneously on 3 non-consecutive days of the week. Patients received 3 MU per dose during the first week, 6 MU per dose the second week and 9 MU per dose thereafter.
Dose escalation was suspended for any patient experiencing grade ≥ 3 hematologic or grade ≥ 2 non-hematologic treatment-related toxicity.

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Dose modifications:

Up to two dose reductions per patient were allowed for toxicity. For sunitinib, doses were reduced to 37.5 mg daily and then 25 mg daily (both on the 4/2 schedule) for toxicity as described in the Table 4 (sponsor's protocol p. 13). IFN-α was reduced to 6 MU 3x/week and then 3 MU 3x/ week also according to Table 4.

Table 4--Dose Modifications for Toxicity

Dose Modifications for SU011248 or IFN-α Associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator[1].	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.
Non-hematologic: cardiac toxicity	Continue at the same dose level.	Continue at the same dose level except in the event of: • Asymptomatic decrease of LVEF by an absolute value of 20% and to below LLN • Non-urgent ventricular paroxysmal dysrhythmia requiring intervention, Withhold dose until toxicity is grade ≤1, then reduce dose by 1 level and resume treatment.	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce the dose by 1 level and resume treatment[2].	Remove from protocol.
Non-hematologic: neurotoxicity	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, then continue at same dose level.	Withhold dose until toxicity is grade ≤1, then reduce the dose by 1 level and resume treatment.	Remove from protocol.
Non-hematologic: fever, chills and "flu-like" symptoms	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose level.	Withhold dose until toxicity is grade ≤2, then reduce the dose by 1 level and resume treatment.

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Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic: hyperamylasemia or hyperlipasemia without clinical symptoms of pancreatitis	Continue at same dose level.	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is grade ≤3 then resume treatment.
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose level[3].	Withhold dose until toxicity is grade ≤2, then reduce the dose by 1 level and resume treatment[4].

1 Recurring grade 3 toxicity requires dose reduction. Grade 4 hyperuricemia and grade 3 hypophosphatemia without clinical symptoms do not require dose interruption and modification.
2 Patients with congestive heart failure must be removed from study.
3 Grade 3 lymphopenia and anemia do not require dose modification. Recurring grade 3 neutropenia or thrombocytopenia persisting for at least 5 days requires dose reduction in the next cycle.
4 Grade 4 lymphopenia does not require dose reduction.

Re-escalation was allowed in the absence of subsequent episodes of severe toxicity. No dose escalations beyond 50 mg of sunitinib or 9 MU of IFN were allowed.

Table 5--Schedule of Assessments:

Protocol Activities and Forms to be Completed	Screening		Cycle 1			Cycles 2-4		Cycles 5 +		Post Treatment		
	≤21 Days Prior to Dosing	≤7 Days Prior to Dosing	Day 1 [1] (–1)	Day 14 (± 3)	Day 28 (± 3)	Day 1 (–1)	Day 28 (± 3)	Day 1 (–1)	Day 28 (± 3)	End of Treatment/ Withdrawal [2]	Post Treatment	Survival Follow-up
Baseline Documentation												
Informed Consent	X											
Medical/Oncologic History [3]	X											
Physical Examination [4]	X		X			X		X		X	(X)	
Baseline Signs/Symptoms			X									
Laboratory Studies [5]												
Hematology [6]	X		X	X	X	X	X	X	X	X	(X)	
Blood Chemistry [7]	X		X	X	X	X	X	X		X	(X)	
Coagulation [8]	X											
Urinalysis [8]	X											
Pregnancy Test [9]	X											
12-lead ECG [10]	X				X*							
MUGA scan	X				X		X Odd cycle		X Odd cycle	X	(X)	
Tumor Assessments [11]												
Tumor Imaging** [13]	X				X		X		X Even cycle	X		
Brain CT or MRI Scan [14]	X											
Bone Scan** [15]	X				(X)		(X)		(X)	(X)		
Other Assessments												
ECOG PS, Body Weight, and Vital Signs [16]	X		X		X	X	X	X	X	X	(X)	
EQ-5D Questionnaire [17]	X		X		X	X	X	X	X	X		
FACT-G/FKSI Questionnaire [17]	X		X		X	X	X	X	X	X		
Study Drug Compliance [18]					X		X		X	X		
Adverse Events [19]			X	X	X	X	X	X	X	X	X	
Concomitant Medications/Treatments [20]	X		X	X	X	X	X	X	X	X	X	
Post-study Survival Status [21]												X
Pharmacokinetic Studies												
Trough Drug Concentration (Ctrough) [22]			X		X*	X	X*					
Soluble Protein Assessment [23]			X		X*	X	X*			X	X	
RNA Expression [24]			X		X*	X	X*			X	X	
Circulating Endothelial Cell Assay [25]			X		X*	C2 only	C2 only*			X	X	
Tumor Biopsy (optional) [26]	(X)											

( ) = if applicable, see footnotes and Section 7
* Day 28 ECGs and PK/PD samples only have – 3 days window.
** Allowable window for tumor assessment imaging studies is ± 7 days.

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Footnotes for Schedule of Events	
1.	**Day 1 of Cycle 1 Assessments:** Hematology and blood chemistry need not be obtained on Cycle 1 Day 1 if a screening sample has been performed within 7 days.
2.	**End of Treatment/Withdrawal:** These assessments do not need to be completed if they have been performed within 7 days of study withdrawal (within the last 6 weeks for tumor assessments and MUGA scan).
3.	**Medical/Oncologic History:** Includes oncologic history, demographics, history of other disease processes (active or resolved) and concomitant illnesses.
4.	**Physical Examination:** Examination of major body systems.
5.	**Central Laboratory:** Samples for hematology, coagulation, and blood chemistry must be sent to the central laboratory. Sites may perform additional local assays for the purposes of planning treatment administration, dose modification, or monitoring adverse events.
6.	**Hematology:** These samples are sent to the central laboratory. See Appendix 1 for required tests.
7.	**Blood Chemistry:** These samples are sent to the central laboratory. See Appendix 1 for required tests.
8.	**Urinalysis and Coagulation:** Tests will be done at screening, then as clinically indicated thereafter; UA to be performed at a local laboratory and coagulation sample to be sent to the central laboratory.
9.	**Pregnancy Test:** Serum or urine test must be performed for all women of childbearing potential. This test will be performed at a local laboratory.
10.	**ECG:** Three consecutive 12-lead ECGs at least 2 minutes apart will be performed at screening and on Cycle 1 Day 28 to determine the mean QTc interval. Attempts should be made for the screening and C1D28 ECGs to be performed in the morning and time-matched (± 1 hour). In the subset of patients with PK sampling, the C1D28 ECGs and C1D28 PK sample should be taken on the same day. If the mean QTc interval is prolonged (>500 msec), the ECGs should be overread by a cardiologist at the site for confirmation. Additional ECGs may be performed as clinically indicated.
11.	**Study Randomization:** Patient number, randomization, and treatment assignment will be obtained via centralized randomization.
12.	**Study Treatment:** Patients randomized to receive SU011248 will self-administer SU011248 orally once daily at 50 mg/day for 4 weeks followed by a 2-week rest period in each cycle. Patients randomized to IFN-α will receive a subcutaneous injection on three non-consecutive days per week (MWF or TThSa), starting at 3 MU per dose during the first week, 6 MU per dose during the second week, and 9 MU per dose thereafter. Patients may continue with therapy until disease progression, unacceptable toxicity, or withdrawal of patient consent.
13.	**Tumor Imaging:** CT or MRI scans of the chest, abdomen, and pelvis and any other applicable sites of disease at screening, Day 28 of Cycles 1, 2, 3, 4, even cycles thereafter, whenever disease progression is suspected, to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the End of Treatment/Withdrawal. All imaging studies indicating response or disease progression will be objectively verified by an independent third-party imaging core laboratory as described in the Study Reference Binder.
14.	**Brain CT or MRI scan:** To be performed at screening only.
15.	**Bone Scan:** To be performed at screening and on Day 28 of Cycles where Tumor Imaging is performed if bone metastases are present.
16.	**ECOG PS, Body Weight, and Vital Signs:** Height at screening only; vital signs to include temperature, blood pressure, heart rate, and respiratory rate.
17.	**EQ-5D and FACT-G/FKSI Questionnaires:** To be completed by patient prior to randomization during the screening period, Days 1 and 28 of each cycle, and at the End of Treatment/Withdrawal. The questionnaires should be completed prior to other clinical assessments.
18.	**Study Drug Compliance:** The study drug including any unused drug will be returned to the clinic for drug accountability at the end of each cycle.
19.	**Adverse Events:** Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Serious adverse events should be monitored and reported from the time that the patient provides informed consent as described in the protocol.
20.	**Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment, during the study, and up to 28 days post the last dose of study treatment. For pharmacoeconomic (cost effectiveness) analysis, the number and length of hospital stays during the study treatment period and up to 28 days post the last dose of study treatment will be collected.
21.	**Post-study Survival Status:** Follow-up survival information will be collected by clinic visit or telephone contact every 2 months until death.
22.	**Trough Drug Concentration (C_{trough}):** A single 4-mL blood sample will be collected pre-dose on the specified days at selected sites only.
23.	**Soluble Protein Assessment:** 10-mL and 4-mL blood samples will be collected pre-dose on the specified days at selected sites only.
24.	**RNA Expression:** Whole blood samples (7.5 mL total) for assessment of potential RNA expression will be collected pre-dose on the specified days at selected sites only.
25.	**Circulating Endothelial Cell Assay:** A 7-mL blood sample will be collected pre-dose on the specified days at selected sites only.
26.	**Tumor Biopsy:** Pre-study biopsy of tumor tissue (or a previously collected paraffin tumor block) is optional at selected sites for correlative laboratory analysis. Repeat tumor biopsies on study are also optional. Refer to the Study Reference Binder for sample processing and shipping instructions.

Criteria for patient withdrawal from treatment:

- Medical necessity
- Patient withdrawal of consent
- RECIST-defined disease progression
- The need for surgery, radiation, or for other anticancer therapy not specified in the protocol
- Congestive heart failure
- The patient is lost to follow-up or noncompliant

Patients were followed for at least 28 days after the last dose of study drug for adverse events. Survival was followed until death.

Statistical Methods:

Study Populations:

The study population for all analyses will be defined as follows:
• Intent-to-Treat Population (Full Analysis Set)

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This population included all patients who were randomized, with study drug assignment designated according to initial randomization, regardless of whether patients received study drug or received a different drug from that to which they were randomized. This was the primary population for evaluating all efficacy endpoints as well as patient characteristics. The analysis of the primary endpoint (PFS) was performed in this population.

- As-Treated Population

  The as-treated population consists of all patients who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints as well as post-study treatment administration were assessed in this population, taking into account the disposition of all patients not eligible for post-study treatment (e.g., patients who die while on study treatment, are still on study treatment, etc.).

Endpoint Definitions:

Progression-free survival (PFS) is defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, whichever occurs first. PFS data were censored on the day following the date of the last on treatment (including 28 day follow-up period) tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression. Patients lacking an evaluation of tumor response after randomization had their event time censored on the date of randomization with a duration of 1 day.

Time to tumor progression (TTP) is defined as the time from randomization to first documentation of objective tumor progression. TTP data were censored on the day following the date of the last on treatment (including 28 day follow-up period) tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression while on treatment or who were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression. Patients lacking an evaluation of tumor response after randomization had their event time censored on the date of randomization with a duration of 1 day.

Overall confirmed objective response rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to the RECIST criteria, relative to the total population of randomized patients. Confirmed responses are those that persist on repeat imaging study $\geq$4 weeks after initial documentation of response.

Overall survival (OS) is defined as the time from randomization to date of death due to any cause. For patients not expiring, their survival times were censored at the last date they are known to be alive. Patients lacking data beyond the day of randomization had their survival times censored at the date of randomization with a duration of one day.

Duration of response (DR) is 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 any cause, whichever occurs first. DR data were censored on the day following the date of the last on treatment (including 28 day follow-up period) tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression. DR was only calculated for the subgroup of patients with objective response.

Study Analyses:

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

For the primary efficacy analysis, PFS in each arm was assessed using Kaplan-Meier methods in the intent-to-treat population and compared with a 2-sided unstratified log-rank test at the α=0.05 significance level. Other time-to-event data were evaluated using Kaplan-Meier methods and log-rank tests.

The proportion of patients who achieve an objective tumor response (PR or CR) was computed for each arm and compared by means of a Chi-square test. Investigators used the standardized RECIST (Response Evaluation Criteria in Solid Tumors) criteria of unidimensional tumor assessment to evaluate lesion size to determine the protocol endpoints of response rate, PFS, and TTP. All imaging studies confirming response or disease progression were submitted to an independent, blinded, third-party imaging core laboratory.

Sample Size Determinations:

According to the sponsor, a recent publication reported a PFS in RCC patients treated with IFN-α as a first-line therapy to be 4.7 months (20 weeks).[8] A 35% improvement (hazard ratio 0.74 [Arm A:Arm B]) in median PFS from 20 weeks to 27 weeks in patients randomized to receive sunitinib was considered to be clinically relevant. A total of 471 patients with progressive disease are required for a 2-sided, unstratified log-rank test with an overall 2-sided significance level of 0.05 and power of 0.90.

Applying a 1:1 randomization and a planned accrual period of 12 months, a minimum follow-up period of 4 months, and an expectation that approximately 5% of patients may be lost to follow-up within 6 months, it was estimated that enrollment of 690 patients was needed in order to observe 471 patients with progressive disease by the end of the minimum follow-up period. The nominal significance level for the interim and final efficacy analyses was to be determined using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule. The final analysis was scheduled to take place when the 471st patient has documented progressive disease. The overall type I error rate will be preserved at the nominal 0.05 level. The sample size described above was also considered adequate to allow the assessment of differences in the secondary endpoint of

OS with a high level of significance. Median OS in RCC patients treated with IFN-α as a first-line therapy is reported to be approximately 13 months (56 weeks). A total of 390 events are required for a 2-sided, unstratified log-rank test with an overall 2-sided significance level of 0.05 and power of 0.85. This assumes a 35.7% improvement (hazard ratio 0.74 [Arm A:Arm B]) in median OS from 56 weeks to 76 weeks in patients randomized to receive sunitinib and a minimum follow-up period of approximately 12 months. The estimated sample size of 690 patients for PFS will also be sufficient to observe the 390 events needed for comparing median OS.

Interim Efficacy and Safety Analysis:

An interim analysis of efficacy and safety was to be performed after the first 250 patients had completed at least 3 cycles of treatment (slightly more than one-third of the total number of patients expected to enroll in the study). At this time it was expected that 147 patients would have documented disease progression (approximately 30% of the total number expected). The nominal level of significance for the interim analysis of PFS was to be determined at the time of the interim analysis using the Lans-DeMets procedure with an O'Brien-Fleming stopping rule. If exactly 147 events had occurred at the time of the interim analysis, then the nominal significance level would have been 0.00012. A second interim analysis was to be performed when approximately 354 events had occurred (approximately 75% of the total number of events expected).

The objectives of the interim analysis were:

- To assess safety, including any unexpected toxicity. If the results of the interim analysis indicated serious safety concerns, the Sponsor planned to consult with Health Regulatory Authorities (HRAs) regarding stopping the clinical trial.
- To compare the ORR between treatment arms. Analysis of response of the first 250 patients had 90% power to detect an improvement in ORR from 11% to 27%.
- To compare median OS between treatment arms. If results of the interim analysis indicated significant differences in survival between treatment arms, the Sponsor planned to consult with HRAs regarding stopping the clinical trial.
- To compare PFS between treatment arms (second interim analysis).

6.1.4 Efficacy Findings

The primary efficacy analysis for this review was the second interim analysis of PFS. Updated ORR data were provided for this analysis.

As of the data cutoff on November 15, 2005, 750 patients had been randomized and comprised the intent-to-treat (ITT) population for the PFS (second interim) analysis. Three hundred and seventy five patients were randomized to either arm.

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Fifteen patients (4%) randomized to IFN-α withdrew from the study prior to receiving study therapy; all patients randomized to sunitinib received protocol treatment. There were no treatment misallocations.

Because the second interim analysis was submitted within several months after the first analysis, and because the second analysis contained more up-to-date response data in a larger population, the PFS analysis and the ORR analysis contained in this review relied primarily on data from the second interim analysis. The first interim analysis patient population did not differ significantly from the second in terms of patient demographics, disease characteristics or response rates.

Protocol Eligibility Violations:

Violations in at least one of the eligibility criteria were reported for 28 (7.5%) of patients randomized to sunitinib vs. 36 (9.6%) of patients randomized to interferon. Most of these violations were laboratory values outside the specified range (including LVEF below normal in eight patients and QTc > 450 msec in nine patients) or failure to perform required laboratory tests or study screening procedures. Ten patients were enrolled despite a history CNS metastases/spinal cord compression. Two patients were reported to have no documentation of clear cell histology.

Patient Demographic characteristics for the ITT population are described in Table 6 and patient disease characteristics and prior therapy are described in Table 7.

Table 6--Patient Demographics and Baseline Characteristics—PFS Population

Variable	Sunitinib N=375	IFN-α N=375
Sex, n (%)		
Male	267 (71)	269 (72)
Female	108 (29)	106 (28)
Race, n (%)		
White	354 (94)	340 (90)
Black	4 (1)	9 (2)
Asian	7 (2)	12 (3)
Not listed	10 (3)	14 (4)
Age, median (years)	62	59
Range	27-87	34-85
<65 years	223 (59)	252 (67)
≥65 years	152 (41)	123 (33)
ECOG performance status*, n (%)		
0	228 (61)	228 (61)
1	147 (39)	147 (39)

*at randomization; some patients had a change in PS prior to initiation of therapy including four on the IFN arm with PS 2

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Table 7--Disease Characteristics and Prior Therapy (PFS population)

Parameter	Sunitinib N=375	IFN-α N=375
Tumor type, n (%)		
Renal cell carcinoma	375 (100)	375 (100)
Histology, n (%)		
Clear cell	334 (89)	339 (90)
Other, clear cell component described	40 (11)	35 (9)
No clear cell component	1 (<1)	1 (<1)
Time from diagnosis to Study entry (weeks), median (range)	45.7 (0.6-1278.7)	44.4 (1.3-1115.1)
Sites of disease, n (%)		
Lung	292 (78)	298 (80)
Lymph nodes	218 (51)	198 (53)
Bone	112 (30)	112 (30)
Liver	99 (26)	90 (24)
Visceral	63 (17)	63 (17)
Local recurrence	63 (17)	56 (15)
Soft Tissue	59 (16)	56 (15)
Primary Tumor	59 (16)	49 (13)
Pleural Effusion	40 (11)	26 (7)
Peritoneal	21 (6)	29 (8)
Number of sites, median (range)	2 (1-7)	2 (0-8)*
Nephrectomy, n (%)		
Yes	340 (91)	335 (89)
No	35 (9)	40 (11)
Radiation Therapy, n (%)	53 (14)	54 (14)

* four pts on IFN had no metastatic sites (2 had primary tumor and 2 local recurrences)

Reviewer's note: The two arms appear to be well balanced for time since diagnosis, median number of disease sites, location of disease, and prior history of nephrectomy and radiation.

Progression-free survival—Sponsor's analysis

For the primary analysis of PFS in the ITT population based on independent review data, there were 96 events (25.6%) of progression or death on the sunitinib arm compared with 154 events (41.1%) of progression or death on the IFN arm. Data from ninety patients, 40 on the sunitinib arm (11%) and 50 on the IFN arm (13%), had not been reviewed by the central laboratory at the time of the analysis. Median PFS was 47.3 weeks (95% CI 42.6, 50.7) for sunitinib-treated patients and 22.0 weeks (95% CI 16.4, 24.0) for patients treated with IFN; the hazard ratio was 0.415 (95% CI .320, 0.539, p<0.000001).

Table 8, derived from the sponsor's interim study report (Table 13, p. 91) describes the results of the time-to-event endpoints PFS and TTP for both the ITT and AT populations, based on both investigator and independent review data.

Table 8—Sponsor's Summary of Time-to-Event Endpoint Results

Table 13. Summary of Time-to-Event Endpoints (ITT and AT Populations)

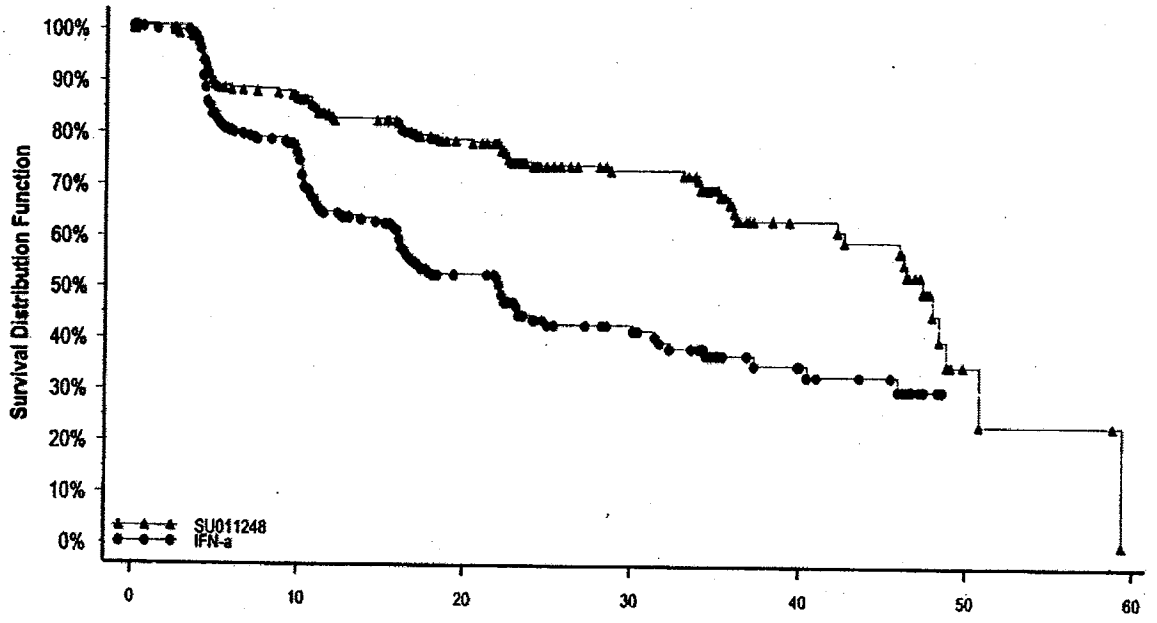
Variable	Number of Events: Sunitinib malate n (%)	Number of Events: IFN-α n (%)	Hazard Ratio	95% CI of Hazard Ratio	p-value
Core Radiology Assessment					
ITT population [N]	375	375			
PFS (events; n [%])	96 (25.6)	154 (41.1)	0.415	(0.320 to 0.539)	< 0.000001
Median (weeks)	47.3	22.0			
95% CI	(42.6 to 50.7)	(16.4 to 24.0)			
TTP (events; n [%])	90 (24.0)	142 (37.9)	0.416	(0.318 to 0.545)	< 0.000001
Median (weeks)	47.9	22.3			
95% CI	(45.9 to 50.7)	(17.3 to 31.3)			
AT population [N]	375	360			
PFS (events; n [%])	96 (25.6)	154 (42.8)	0.415	(0.320 to 0.539)	< 0.000001
Median (weeks)	47.3	22.0			
95% CI	(42.6 to 50.7)	(16.4 to 24.0)			
TTP (events; n [%])	90 (24.0)	142 (39.4)	0.416	(0.318 to 0.545)	< 0.000001
Median (weeks)	47.9	22.3			
95% CI	(45.9 to 50.7)	(17.3 to 31.3)			
Investigators' Assessment					
ITT population [N]	375	375			
PFS (events; n [%])	118 (31.5)	193 (51.5)	0.416	(0.330 to 0.524)	< 0.000001
Median (weeks)	45.7	17.3			
95% CI	(35.7 to 59.3)	(16.3 to 22.4)			
TTP (events; n [%])	114 (30.4)	185 (49.3)	0.415	(0.328 to 0.526)	< 0.000001
Median (weeks)	45.7	18.0			
95% CI	(36.0 to 59.3)	(16.6 to 23.1)			
AT population [N]	375	360			
PFS (events; n [%])	118 (31.5)	193 (53.6)	0.416	(0.330 to 0.524)	< 0.000001
Median (weeks)	45.7	17.3			
95% CI	(35.7 to 59.3)	(16.3 to 22.4)			
TTP (events; n [%])	114 (30.4)	185 (51.4)	0.415	(0.328 to 0.526)	< 0.000001
Median (weeks)	45.7	18.0			
95% CI	(36.0 to 59.3)	(16.6 to 23.1)			

Reviewer's note: the ITT and AT population differ only with respect to 15 patients who were randomized to interferon but never received study drug. There were no treatment misallocations (all treated patients received the treatment to which they were randomized).

The Kaplan-Meier curve of PFS is presented in Figure 1 (figure 2 of the sponsor's study report.)

Figure 1—Kaplan-Meier Curve of Progression-Free Survival

Figure 2. Kaplan-Meier Curve of Progression-Free Survival by Treatment (Core Radiology Assessment, ITT Population)



Number of subjects at risk

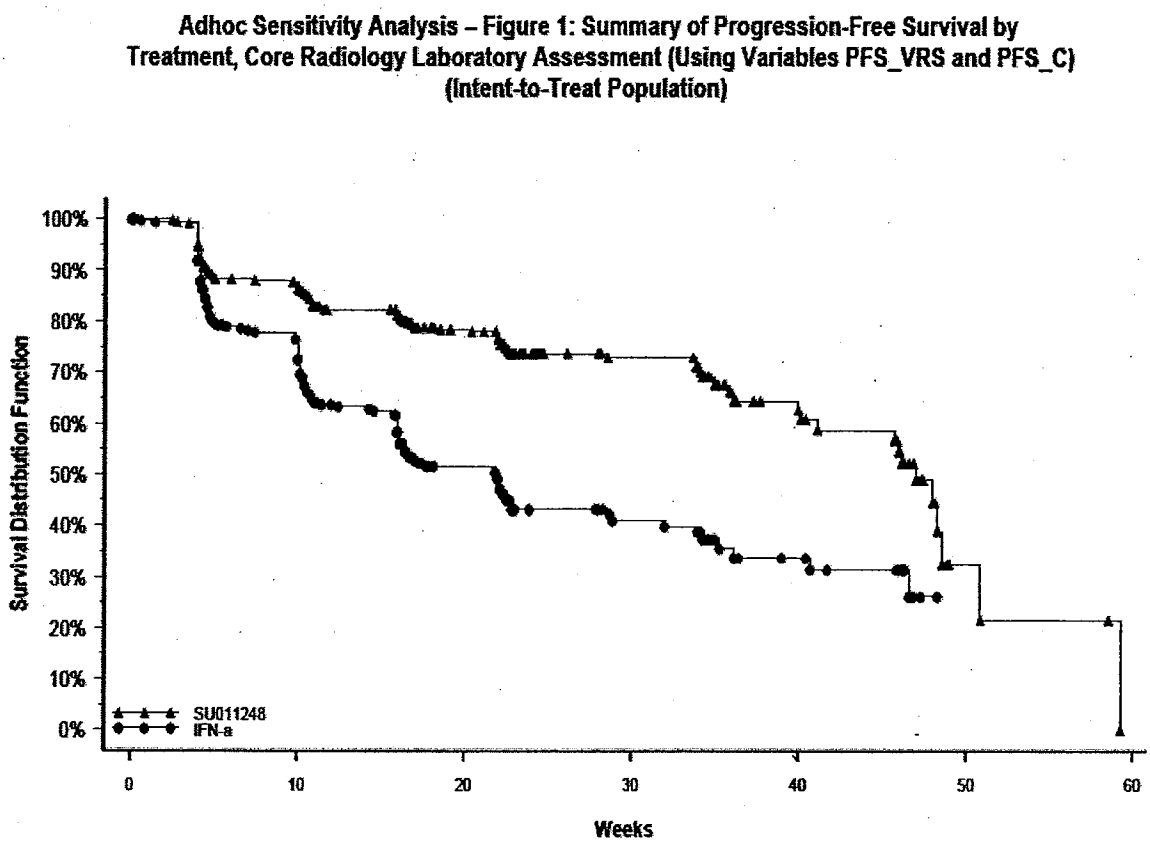
Sunitinib:	375	274	173	84	31	3	0
IFN-α	375	207	84	38	16	0	0

Source: Figure 14.1.1.1.1 and Appendix A10.2.1.1.1

At the request of the FDA statistical reviewer team, the sponsor also conducted three sensitivity analyses of PFS, which were submitted to the NDA on 11/21/06. The first was done to evaluate any potential bias in assessment of progression due to unscheduled visits. In this assessment, PFS events/censoring (except deaths) only occurred on scheduled visit dates. This analysis resulted in a median PFS of 47.0 weeks for the sunitinib arm and 22.0 weeks for the IFN arm (HR 0.421, 95% CI 0.324, 0.546). The Kaplan-Meier curve for this analysis is shown in Figure 2 below.

b(4)

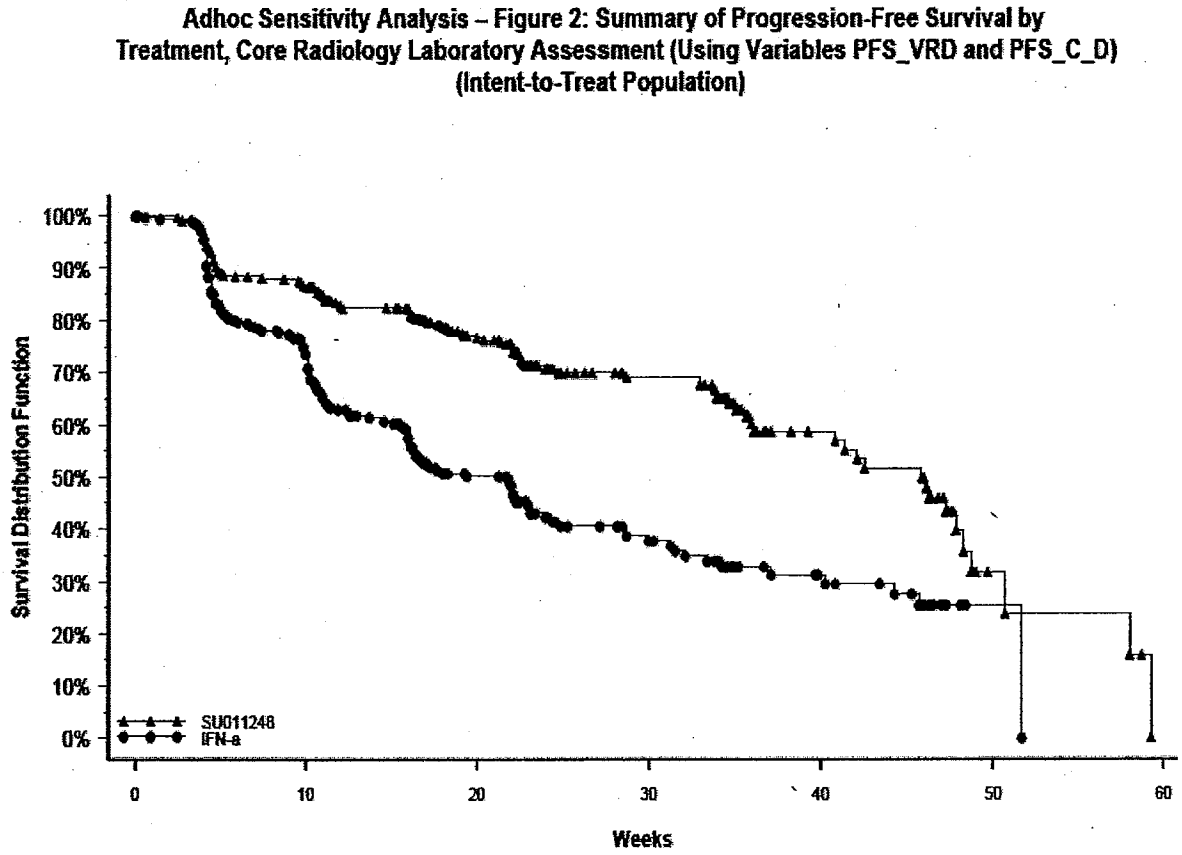
Figure 2—Sensitivity Analysis of PFS Using Scheduled Visit Dates for Progression Events/Censoring



The second sensitivity analysis included deaths occurring after a patient was off-study (more than 28 days after the last drug dose) as events, rather than censoring them as in the primary analysis. This analysis resulted in a median PFS of 45.9 weeks for the sunitinib arm and 21.9 weeks for the IFN arm (HR 0.434, 95% CI 0.340, 0.553). The Kaplan-Meier curve for this analysis is shown in Figure 3 below.

b(4)

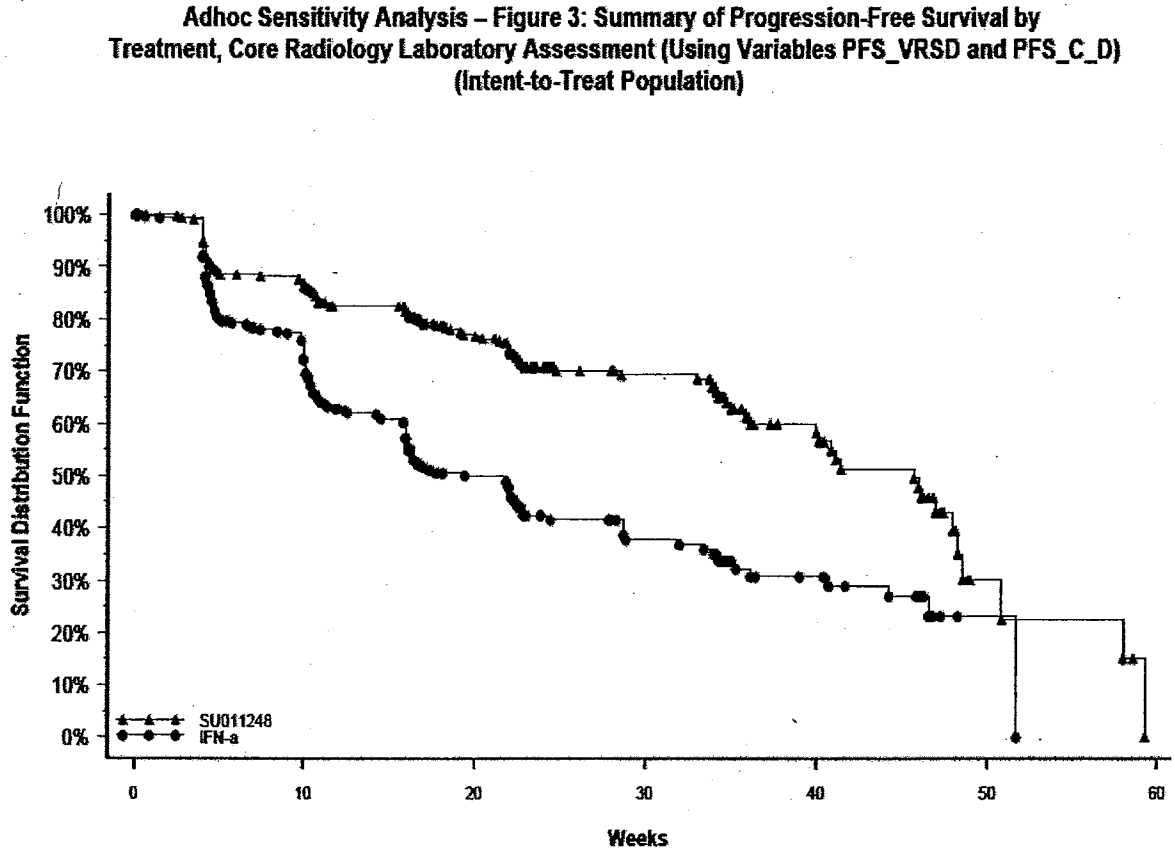
Figure 3--Sensitivity Analysis of PFS Including All Deaths as Events



The third sensitivity analysis included both of the above parameters (i.e. all events/censoring except deaths at scheduled visits and off-study deaths included as events.) This analysis resulted in a median PFS of 45.7 weeks for the sunitinib arm and 19.4 weeks for the IFN arm (HR 0.438, 95% CI 0.344, 0.559). The Kaplan-Meier curve for this analysis is shown in Figure 4 below.

b(4)

Figure 4: Sensitivity Analysis of PFS Including Both All Deaths and Progression Events/Censoring Only on Scheduled Visit Dates



These data further support the conclusion that treatment with sunitinib improves progression-free survival compared to treatment with interferon in patients with metastatic renal cell carcinoma.

Progression-free survival—FDA analysis

PFS was reviewed in the primary efficacy population based on the independent review data. Data tables reviewed for this analysis included RADLSN, and END. Appendix B4.4.1.1, which contains a listing of individual patient PFS data, was reviewed. Table 13.6.4.2 of the study report (pp. 1486-1510), which contains a listing of subjects who died and cause of death, was also reviewed.

Progression of disease was reviewed in the RADLSN database. Patients were assessed as having disease progression if (1) the sum of the longest diameters of the target lesions increased by 20% or greater from the nadir, (2) there was progression in non-target lesions, and/or (3) new lesions occurred.

Using these criteria, the sponsor's report of the number of PFS events was evaluated. Ninety patients on the sunitinib arm and 142 patients on the IFN arm had disease progression as the PFS event. Deaths were counted as PFS events if they occurred "on study" or up to 28 days following drug discontinuation. Death was the PFS event for 6 sunitinib-treated patients and 12 IFN treated patients.

In addition to the number of events in either arm, dates of progression and death were confirmed, and the time to PFS endpoint calculation was confirmed using the PFS event date and the randomization date. For patients who reportedly died due to "progressive disease" as the PFS event, prior radiographic exams were reviewed to ensure that they did not meet RECIST criteria for progressive disease prior to death. No discrepancies were found in any of these variables. Thus, the sponsor's report of PFS events was confirmed as accurate.

An audit of the radiographic data by FDA's Division of Medical Imaging and Hematology Products (DMIHP) was not performed for this supplement. DMIHP conducted an audit of the radiographic data for the original sunitinib NDA (both RCC and GIST) indications and found no significant discrepancies. The independent contractor used by the sponsor for this supplement was the same (———— , used for the original NDA. Given the blinded nature of the third-party review, as well as the prior experience with ———— an audit was felt to be unnecessary. b(4)

Analyses of PFS by gender, age and race were performed by the statistical reviewer, Dr. Shengui Tang. Unadjusted log-rank tests were performed for each subgroup. All subsets of patients evaluated appeared to benefit. Tables 9, 10, and 11 describe the findings based on gender, age and race, respectively.

Table 9—PFS Analysis by Gender

	Sunitinib	IFN-α
Gender		
Male		
Number of patients (ITT)	267	269
Number of events (%)	72 (27.0%)	103 (38.3%)
Median (weeks), 95% CI[1]	47.9 (42.1, 48.7)	22.3 (17.1, 40.3)
Hazard ratio [95% CI][2]	0.47 (0.35, 0.64)	
Unadjusted log-rank test	P-value[3]<0.00001	
Female		
Number of patients (ITT)	108	106
Number of events (%)	24 (22.2%)	51 (48.1%)
Median (weeks), 95% CI[1]	46.3 (46.1, 50.7)	16.0 (10.3, 22.1)
Hazard ratio (95% CI)[2]	0.30 (0.18, 0.49)	
Unadjusted log-rank test	P-value[3]<0.00001	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm; [3]: not adjusted for multiple analyses.

b(4)

Table 10—PFS Analysis by Age

	Sunitinib	IFN-α
Age		
<65		
Number of patients (ITT)	223	252
Number of events (%)	63 (28.3%)	108 (42.9%)
Median (weeks), 95% CI[1]	46.3 (42.1, 48.3)	17.3 (16.0, 23.0)
Hazard ratio (95% CI)[2]	0.41 (0.30, 0.56)	
Uadjusted log-rank test	P-value[3]<0.00001	
>=65		
Number of patients (ITT)	152	123
Number of events (%)	33 (21.7%)	46 (37.4%)
Median (weeks), 95% CI[1]	48.7 (35.7, -)	23.1 (16.4, 34.3)
Hazard ratio (95% CI)[2]	0.43 (0.28, 0.69)	
Uadjusted log-rank test	P-value[3]=0.0002	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm; [3]: not adjusted for multiple analyses.

Table 11—PFS Analysis by Race

	Sunitinib	IFN-α
Race		
White		
Number of patients (ITT)	354	340
Number of events (%)	87 (24.6%)	138 (40.6%)
Median (weeks), 95% CI[1]	46.3 (42.1, -)	22.1 (16.4, 24.9)
Hazard ratio [95% CI][2]	0.42 (0.32, 0.56)	
Unadjusted log-rank test	P-value[3]<0.00001	
Non-white		
Number of patients (ITT)	21	35
Number of events (%)	9 (42.9%)	16 (45.7%)
Median (weeks), 95% CI[1]	48.3 (42.6, 59.3)	17.7 (9.9, -)
Hazard ratio (95% CI)[2]	0.35 (0.13, 0.98)	
Unadjusted log-rank test	P-value[3]=0.0362	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm; [3]: not adjusted for multiple analyses.

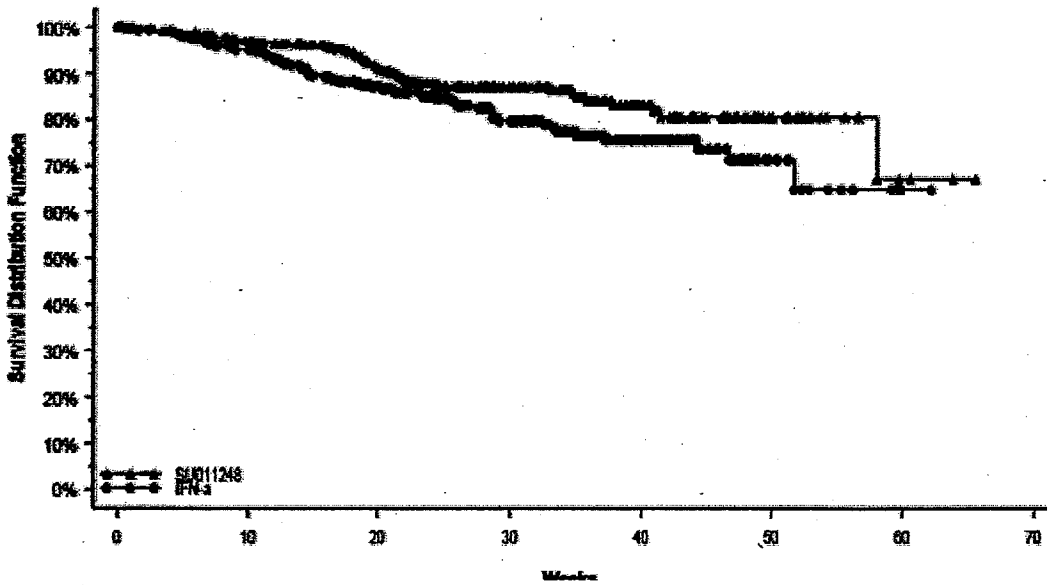
Overall Survival

Overall survival data were not mature at the time of the second interim analysis, with the median not yet reached on either arm. The hazard ratio for OS was 0.650 (95% CI: 0.449 to 0.942; p = 0.0219); which was not statistically significant based on the stopping boundaries for this interim analysis.

b(4)

The sponsor's Kaplan-Meier analysis of the OS data is presented in Figure 5 (sponsor's figure 14.1.3.1.1).

Figure 5—Kaplan-Meier Analysis of OS in the ITT Population



Response rate—Sponsor's analysis

Response rate was analyzed by the sponsor in both the ITT and AT populations, based on both investigator and independent review data. Responses were evaluated based on RECIST criteria. Briefly, evaluations including target (measurable) lesions, non-target lesions and evaluation for new lesions. To be considered a partial response, a reduction of at least 30% in the sum of the longest diameter of all target lesions must be achieved, in the setting of stable disease or better in non-target lesions and the absence of new lesions. Responses must be confirmed at least 4 weeks after initial documentation of response.

These data are summarized in Table 12 (derived from Table 14 on p. 92 of the study report).

b(4)

Table 12—Sponsor's Summary of Objective Response Rate Data

Table 14. Summary of Overall Objective Response Rate (ITT and AT Populations)

Variable	Treatment: Sunitinib malate n (%)	Treatment: IFN-α n (%)	Treatment Difference (%)	p-value[a]
Core Radiology Assessment[b]				
ITT population [N]	375	375		
ORR	103 (27.5)	20 (5.3)	22.13	< 0.001
95% CI[c]	(23.0 to 32.3)	(3.3 to 8.1)	(17.08 to 27.19)	
AT population [N]	375	360		
ORR	103 (27.5)	20 (5.6)	21.91	< 0.001
95% CI[c]	(23.0 to 32.3)	(3.4 to 8.4)	(16.81 to 27.01)	
Investigators' Assessment				
ITT population [N]	375	375		
ORR	137 (36.5)	33 (8.8)	27.78	< 0.001
95% CI[c]	(31.7 to 41.7)	(6.2 to 12.2)	(22.11 to 33.45)	
AT population [N]	375	360		
ORR	137 (36.5)	33 (9.2)	27.44	< 0.001
95% CI[c]	(31.7 to 41.7)	(6.4 to 12.7)	(21.71 to 33.16)	

a From a Pearson χ^2 test.
b Core radiology results were missing for 90 subjects (40 [10.7%] vs 50 subjects [13.3%] on sunitinib malate vs IFN-α, respectively); in most cases the data were missing because scans had not been sent or were available but had not yet been read by the core radiologist.
c Exact method based on binomial distribution for ORR; based on a normal distribution for treatment difference

All responses were partial responses, with a response rate of 27.5% in the sunitinib treated population compared to 5.3% in the IFN treated population in the primary analysis population.

Response rate—FDA analysis

Response rate was evaluated by the reviewer in the ITT population using the blinded, third-party review data (data source: [redacted] LSN data set). Using the criteria outlined above for partial responses, all patients who achieved a 30% or greater reduction in the sum of the longest diameter of all target lesions were identified. These were counted as partial responses if: (1) the non-target lesion evaluation was SD or better, (2) no new lesions were identified, and (3) the response was confirmed on a second consecutive evaluation at least 4 weeks after the prior evaluation. The ORR data are summarized in Table 13.

b(4)

Table 13– FDA Analysis of ORR

	Sunitinib N=375	IFN-α N=375
ORR, n (%)	103 (27.5)	20 (5.3)
95% CI	23.0, 32.3	3.3, 8.1

b(4)

Comment: The response rate on the sunitinib arm is consistent with that seen in the two single-arm trials of patients with cytokine-refractory renal cell carcinoma.

Response rate from study A6181006:
Study A6181006 is a single-arm trial performed in patients with cytokine-refractory MRCC. This study was reviewed under the initial NDA for sunitinib (NDA 21-968) submitted in August, 2005. The sponsor updated the response rate during the review process; however, the data tables supporting the improved ORR were not provided. These data tables were therefore the subject of a post-marketing commitment and are reviewed here.

The updated data include an ORR of 34% (36/106, all partial responses, 95% CI 25.0, 43.8) as evaluated by the core radiology laboratory, which was the protocol-specified primary analysis. Duration of response data are not mature (the median has not been reached with nine failures and 27 censored patients); the lower bound of the 95% CI was reported as 42 weeks. Of the 36 partial responses, the data supporting 27 of these was reviewed with the August 2005 submission. The data supporting the nine additional responses were reviewed as part of this submission. Tables reviewed in JMP included — TLSN, — NTLSN, — NWLSN (for target lesions, non-target lesions, and new lesions, respectively). All patients were confirmed to have achieved a 30% reduction in the sum of the largest diameters, confirmed on two subsequent exams at least 4 weeks apart, with no new lesions or progression of non-target lesions noted. Progression dates (when documented) were confirmed through this analysis as well. Duration of response was also confirmed as immature based on the updated response and progression data.

b(4)

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Study A6181034 is a randomized, open label trial in patients with treatment-naïve metastatic renal cell carcinoma. The efficacy evaluation was based on the second interim analysis of the study, which primarily analyzed PFS and also evaluated ORR. Seven hundred and fifty patients were randomized 1:1 to receive either sunitinib or IFN-α. Sunitinib was given at a starting dose of 50 mg orally once daily for 4 weeks, followed by a two week rest period (4/2 schedule). IFN-α was given subcutaneously on three nonconsecutive days per week at a starting dose of 3 MU per dose during the first week, 6 MU per dose the second week and 9 MU per dose thereafter.

Three hundred and seventy five patients were randomized to each arm. The two treatment arms were well balanced for baseline demographic characteristics, including age, gender, and race. Patients were required to have some component of clear cell histology and most (90%) had undergone prior nephrectomy. The median number of sites of disease was two: common sites included lung, lymph nodes, bone and liver.

b(4)

For the primary analysis of PFS in the ITT population based on independent review data, there were 96 events (25.6%) of progression or death on the sunitinib arm compared with 154 events (41.1%) of progression or death on the IFN arm. Median PFS was 47.3 weeks (95% CI 42.6, 50.7) for sunitinib-treated patients and 22.0 weeks (95% CI 16.4, 24.0) for patients treated with IFN; the hazard ratio was 0.415 (95% CI .320, 0.539, $p<0.000001$). These results were supported by three sensitivity analyses of PFS. Overall survival data were not mature at the time of the second interim analysis.

Overall response rate was also improved on the sunitinib arm compared to the IFN arm, with an ORR of 27.5% (95% CI 23.0%, 32.3%) vs. 5.3% (95% CI 3.3%, 8.1%). The response rate noted on the sunitinib arm is similar to the response rates seen in two single-arm trials of sunitinib in patients with cytokine-refractory MRCC.

The updated response data from study A6181006 include an ORR (all partial responses) of 34% (95% CI 25.0, 43.8) as evaluated by the core radiology laboratory, which was the protocol-specified primary analysis. Duration of response data are not mature (the median has not been reached with nine failures and 27 censored patients); the lower bound of the 95% CI was reported as 42 weeks.

The improvement in PFS demonstrated in study A6181034 is a clinically and statistically significant finding which provides evidence of clinical benefit in patients with MRCC.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The primary source of data for the safety review was the safety database from study A6181034 and included evaluation of adverse events, laboratory, and vital signs data. Left ventricular ejection fraction data were also analyzed to further evaluate cardiac toxicity. Additional data provided as part of a post-marketing commitment on cardiac toxicity in a single-arm MRCC trial was also evaluated.

7.1.1 Deaths

There were thirteen on-study deaths in the sunitinib safety population and seventeen in the IFN safety population. For one patient in each arm, death occurred on study, following data cutoff but was included in the safety database.

Ten of the sunitinib deaths were attributed to disease progression. The deaths of the three sunitinib patients not attributed to disease progression are described below.

Pt. 208 was a 67 year old woman with an intact primary tumor, liver, lung and lymph node metastases and pleural effusion and a history of type 2 diabetes, HTN and hypercholesterolemia

b(4)

who developed respiratory failure during the first cycle. The investigator attributed the event of fatal respiratory arrest to progressive disease.

Pt. 436 was a 70 year old male s/p left radical nephrectomy who had developed local recurrence and metastases to liver and thorax as well as a pleural effusion and ascites. Medical history was also significant for diabetes and hypertension. Baseline LVEF was > 65% and ECGs were reportedly "abnormal" but not clinically significant. Baseline QTc was 320-370 msec. The patient began sunitinib on 5/10/05 and died suddenly on ———. The cause of death is unknown.

b(6)

Pt. 550 was a 64 year old woman with local recurrence, adrenal and lymph node metastases. She began sunitinib on June 14, 2005 and obtained a partial response, first documented on August 24 and confirmed on Oct 4. There were no adverse events reported until cycle 4, when she was reported to have a gastric ulcer on Oct. 20. She subsequently died due to gastric bleeding on ———. No concomitant medications were recorded. Laboratory data indicate that she did not experience significant thrombocytopenia while on-study. Baseline platelet count was 304, and the cycle 4 count was 255. Platelets never fell below 114 while she was on study.

b(6)

In the IFN safety population, thirteen patient deaths were attributed to disease progression. Other causes of death were reported as suspected cardiac event, myocardial infarction, respiratory failure, dyspnea and cerebral hemorrhage.

7.1.2 Other Serious Adverse Events

One hundred and seventeen patients on the sunitinib arm experienced one or more non-fatal SAEs. The most commonly reported SAEs (# of patients) other than disease progression included vomiting (11), dehydration (9), hypertension (8—includes one malignant hypertension), nausea (8), weakness (7), pleural effusion (7), anemia (6), abdominal pain (6), dyspnea (7—includes one shortness of breath), hyponatremia (5), thrombocytopenia (6), renal failure/insufficiency (5), spinal cord compression (4), pulmonary embolism (4), asthenia (3), back pain (3), confusion (3), fatigue (3), fever (3).

Fifteen bleeding/hemorrhagic events were reported as non-fatal SAEs on the sunitinib arm. These included epistaxis (4), hematuria (3), GI bleeds (4), metrorrhagia (1), cerebral hematoma (1), urinary bladder hemorrhage (1) and hemorrhoids (1). Cardiac SAEs included reduction in ejection fraction (3), myocardial infarction (2), myocardial ischemia (1), cardiac arrest (1), coronary disease (1) and atrial fibrillation (1).

Other notable SAEs on the sunitinib arm included: pancreatitis (2 cases, one reportedly due to gallstones), cholecystitis (2) and reversible posterior leukoencephalopathy syndrome (1).

Seventy patients on the interferon arm experienced one or more non-fatal SAEs. The most commonly reported SAEs (# of patients) other than disease progression included anemia (12), dyspnea/shortness of breath (11), fatigue (5), pathologic fracture (4), pulmonary embolism (4),

b(4)

renal failure (3—includes one creatinine increased), chest pain (3), pulmonary edema (2), pleural effusion (2), septicemia (2), vomiting (2) and urinary retention (2).

Bleeding SAEs occurred in 4 patients and included rectal bleeding, cerebral hemorrhage, hemoptysis and hematuria. Cardiac SAEs included myocardial infarction (2), suspected cardiac event (1) and pericardial effusion (1).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 79 patients were withdrawn from study drug due to non-fatal adverse events: thirty-five on the sunitinib arm (9 %) and 44 on the IFN arm (12%).

7.1.3.2 Adverse events associated with dropouts

Fatigue was the most common AE leading to drug withdrawal (twenty patients on IFN- α and four on sunitinib). Other important reasons for drug discontinuation on the sunitinib arm were cardiac [cardiac arrest (1), CHF (1), myocardial infarction (2), ejection fraction decreased (2), QTc prolongation(1)], vascular [hypertension (1), malignant hypertension (1), pulmonary embolism (1), retinal artery occlusion (1), superior vena caval occlusion (1)], reversible posterior leukoencephalopathy syndrome (1), neutropenia (2), thrombocytopenia (1), renal failure (2), respiratory arrest (1), Stevens Johnson syndrome (1), TTP (1) and ITP (1).

7.1.3.3 Other significant adverse events

Dose modifications due to adverse events:

One hundred and eighty-five patients (49%) treated with sunitinib vs. 130 patients (36%) treated with IFN- α had dose reductions or interruptions due to adverse events. The most common reasons for these dosing modifications in patients treated with sunitinib included gastrointestinal disorders (including nausea, diarrhea and vomiting) in 63 patients (17%), general disorders (including fatigue and asthenia) in 58 patients (15%), investigations in 48 patients (13%), blood and lymphatic system disorders (including thrombocytopenia and neutropenia) in 37 patients (10%), metabolism and nutrition disorders in 27 subjects (7%), skin and subcutaneous tissue disorders (including PPDE) in 26 patients (7%), and respiratory, thoracic and mediastinal disorders in 21 patients (6%). For patients treated with IFN- α, the most common reasons included general disorders in 63 patients (18%), investigations in 24 patients (7%) and blood and lymphatic system disorders in 18 patients (5%).

LVEF changes and congestive heart failure:

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Per protocol, left ventricular ejection fraction was evaluated by MUGA at screening/baseline, on day 28 of odd numbered cycles and at end of study.

All patients on study had screening/baseline evaluations. Four patients (one on the sunitinib arm and three on the IFN arm) had LVEF < 50% on baseline MUGAs. All these abnormalities were mild (LVEF ≥ 48%). An additional three patients on the IFN- α arm had an LVEF > 50% but less than the institutional lower limit of normal.

Seventy-eight patients (21%) receiving sunitinib and 41 patients receiving IFN- α (11%) had an LVEF of below the institutionally defined lower limit of normal while on study. Five of these patients (one on the sunitinib arm and four on the IFN- α arm) had an abnormal baseline LVEF and abnormal LVEF while on study. Among patients with a normal baseline EF, 66 (18%) patients treated with sunitinib and 30 (8%) patients treated with IFN had an LVEF of < 50% at some time while on study. These changes occurred at a median of 29 days for patients receiving sunitinib (range: 12-280) and within the first month in 39 patients. These changes occurred at a median of 30 days for patients receiving IFN (range: 24-196) and within the first month in 16 patients.

An analysis of all patients who had an LVEF of >20% less than baseline and to <50% (LLN) was performed. These patients have both a significant drop in LVEF and an LVEF that falls below the lower limit of normal and thus are the most likely to have "clinically significant" changes. Thirteen (4%) patients on sunitinib vs. 4 (1%) on IFN- α met these criteria at some point on study. The observed changes in LVEF occurred at a median of 111 days (range: 21-207) after the start of sunitinib; however, the event occurred during the first month of treatment in six patients. On the IFN arm, these changes occurred at a median of 122 days (range: 112 to 194) and in no case occurred during the first month.

For the sunitinib-treated patients with LVEF decreases of > 20% and to less than 50%, past medical history, concomitant medications (both at baseline and added during the study), reported adverse events, treatment interruptions and dose modifications were examined, and are summarized in Table 14.

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Table 14—Sunitinib-Treated Patients with LVEF Declines > 20% and to < 50%

Pt. #	Age Sex	B/L LVEF (%)	Lowest LVEF (%)	Action taken	Comment	Relevant PMHx/Medications*
18**	63 M	62 9/28/04	35 1/28/05	Dose reduced to 37.5 mg	LVEF 55% 4/25/05	CAD, hyperlipidemia, HTN, angioplasty Meds: metoprolol, valsartan, atorvastatin, ASA
205**	60 F	66 2/8/05	38 8/30/05	Dose reduced from 37.5 mg to 25 mg	f/u MUGA 9d later EF 61%, dose reduction AFTER this	hyperlipidemia
209	55 M	65 2/7/05	43 6/6/05	1 week interruption and dose reduction to 37.5 mg	LVEF 3 m later 68%	HTN--lisinopril
220	60 F	61 2/7/05	25 3/9/05	Drug discontinued permanently	Pt. had MI—see narrative below	HTN--HCTZ
271	73 M	60 3/1/05	38 10/4/05	None (dose already reduced to 37.5 mg)	No follow-up LVEF (last study 10/4/05) LVEF 60→49→44→38	hypercholesterolemia
331^	71 M	63 3/16/05	42 4/29/05	None	LVEF during study: 63→42→57→63→50→50→ 44→56 from 3/16 to 11/9	Hyperlipidemia, HTN, CVA, LBBB, ischemic CM, PVD, CAD, afib Meds: amiodarone, carvedilol, warfarin, irbesartan, fluvastatin, ezetimibe, Omega-3
392	69 M	54 4/22/05	32 8/12/05	Treatment delayed 1 week and dose reduced to 37.5 mg	LVEF 50% 4 weeks later	HTN, peripheral edema, CVA Meds: Dyazide (added on-study)
456	47 M	62 5/11/05	26 9/16/05	Dose reduced to 37.5 mg	LVEF 67% 2 weeks later	HTN—lisinopril, HCTZ
461	49 M	54 5/12/05	31 9/8/05	Dose decreased to 37.5 for C1 LVEF 44%; ↑ to 50 and ↓ to 37.5 for this event; atorvastatin added on-study	No subsequent LVEF data	Hyperlipidemia, obesity Meds: simvastatin
483	73 M	68 5/3/05	47 6/20/05	Drug permanently w/d† Amlodipine and metoprolol added for HTN	LVEF 65% 10 days later	Chest pain, dyspnea Meds: ASA
525	66 M	51 6/2/05	25 7/5/05	Dose reduced to 37.5 mg at next cycle (not clearly attributed to LVEF change)	LVEF 50% 9/29/05	CAD s/p MI, angina, HTN, hypercholesterolemia, CABG Meds: Dyazide, lovastatin, diltiazem, NTG
637	65 M	53 6/20/05	30 7/26/05	Drug permanently w/d	No follow-up LVEF data; pt. had MI on [redacted]	No cardiac history or meds
643	27 M	60 6/16/05	36 8/2/05	Drug discontinued after first cycle for PD (documented on 8/1/05)	Death d/t PD [redacted]	No cardiac history or meds

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*includes both baseline medications and those added prior to the abnormal LVEF
† AE table shows drug w/d 6/19 d/t fatigue, although event fatigue occurred on 7/1
** patient experienced treatment-emergent hypothyroidism on study

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^ patient had no report of hypothyroidism, but was started on Synthroid while on study

Patient 220 was a 60 year old woman with a baseline LVEF of 61% and a history of hypertension controlled with hydrochlorothiazide. Baseline blood pressure was 109/80. She began treatment with sunitinib on 2/16/05. On 3/6/05, sunitinib was discontinued following a diagnosis of myocardial infarction. LVEF was evaluated by MUGA on 3/9/05 and was 25%. Following the MI, she was placed on nitroglycerin (started in March, 2005), nifedipine and ramipril (start date 4/2/05). A follow-up MUGA was performed on 6/6/05 and demonstrated an LVEF of 65%.

None of these patients has symptoms of congestive heart failure such as peripheral edema or weight increased reported as AEs. While 9 (69%) of them had fatigue reported as an AE, fatigue was also very commonly reported (58%) in the sunitinib treated population as a whole.

Of note, three patients had an adverse event of hypothyroidism and/or had thyroid replacement therapy added while on study. While the effects of the hypothyroid state on cardiac contractility are described[7]; the role of hypothyroidism in the LVEF changes in these patients is unclear. It is also unknown whether unrecognized subclinical hypothyroidism may play a role in the changes in ejection fraction which occur in a subset of patients treated with sunitinib.

Congestive heart failure and left ventricular dysfunction were reported as AEs in one and three patients treated with sunitinib, respectively. LV dysfunction events were grade 1 and 2, the single patient (pt. 281) with CHF had a grade 3 event. On the interferon arm, one patient was reported to have right ventricular dysfunction (grade 3) as an AE, and none developed congestive heart failure. Peripheral edema was more common in sunitinib treated patients (12% vs. 4%); because the incidence was higher than 10%, this is reported in section 7.1.5.4.

The sponsor also submitted additional data on several patients from study A6181006, in partial fulfillment of a post-marketing commitment (PMC). Several patients on this study had a markedly abnormal LVEF as the last available measurement. The sponsor was 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 was asked to submit LVEF data and clinical narratives for any patient who, after the data cutoff for that submission, had a documented LVEF of $\leq$ 40% and/or signs and symptoms of cardiac failure. The specific requests of the PMC are documented below:

- 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.

Data from the requested case narratives were reviewed and are summarized below.

- Patient 63 had a baseline LVEF of 51%, which dropped to 40% in cycle 10. The patient had a history of hypertension. No symptoms suggestive of CHF were reported and no action was taken with respect to study drug as a result of this event. The drug was subsequently discontinued due to lack of efficacy and the patient had no further LVEF data.

- Patient 58 had a history of hypertension and a baseline LVEF of 50%. On study LVEF was ≥ 49% until cycle 10 day 28 when the LVEF was 39%. Blood pressure at that time was 165/91. The subject had trace pedal edema throughout the study period and no worsening of the edema was reported. The cycle 11 dose was reduced to 37.5 mg; it is unclear if this was related to the reduction in LVEF.

- Patient 46 had a baseline LVEF of 57%. LVEF was 37% in cycle 2, 43% in cycle 3, 39% in cycle 4 and 43% in cycle 6. Bilateral ankle edema was reported shortly before the cycle 6 MUGA. The sunitinib dose was reduced twice, to 37.5 mg in response to the cycle 3 LVEF and to 25 mg in response to the cycle 4 LVEF. During cycles 8, 10, and 12, LVEF was 60^, 612% and 60%, respectively.

- Patient 16 had a baseline LVEF of 51% and a history of hypertension. He experienced a decrease in LVEF to 38% in cycle 2 and to 29% in cycle 6. Treatment was delayed and the dose reduced in response to the second event. During cycle 8 his LVEF was 43%. One week later, he was hospitalized and treated surgically for spinal cord compression; an ECG on admission showed changes consistent with anterolateral myocardial infarction, which went unrecognized at that time. No further LVEF data are available; however, the patient was considered "recovered" from reduced LVEF 71 days after his last dose.

- Patient 81 had a history of hypothyroidism and hyperlipidemia and a baseline LVEF of 65%. Cycle 4 LVEF was 37%. LVEF results in cycles 2, 6, 8 and 10 were all above 50%. There were no associated heart failure symptoms during the cycle 4 event and no modifications in study medication were made as a result of the event.

- Patient 92 had a history of hypercholesterolemia and a baseline LVEF of 57%. Cycle 2 and 4 LVEF was 50%; in cycle 6, LVEF dropped to 37%. The sunitinib dose was reduced to 37.5 mg in response to this event. No CHF symptoms were reported. LVEF was 50% in cycle 8 and 45% in cycle 10.

- Patient 94 had a history of aortic stenosis, hypertension, dyspnea on exertion and myocardial infarction. Baseline LVEF was 63%; subsequent LVEF was 47-54% through cycle 8. Cycle 10 LVEF was 38%. Edema of the lower extremities and dyspnea on exertion were reported as ongoing at the time of the event. No additional LVEF data are available and it is unclear whether the dose was modified in response to the event.

- Patient 98 had a baseline LVEF of 56% and no prior history of cardiac disease. LVEF dropped to 42% in cycle 6 and to 40% in cycle 8. Dose of the drug was reduced twice in response to other adverse events (non-cardiac). There were no reported cardiac symptoms.

In summary, changes in left ventricular ejection fraction, including those most likely to be clinically significant, were more common in patients treated with sunitinib than in patients treated with IFN. Many of these patients have a prior history of cardiovascular disease. In most cases, LVEF recovers following dose interruption, reduction, or in some cases, no action with respect to study drug. While relatively few patients were reported to have CHF or left ventricular dysfunction, this was also more common in patients treated with sunitinib, as was the incidence of peripheral edema. Although a causal link has not been established, the coincident occurrence of hypothyroidism in 3/13 sunitinib-treated patients with the most severe changes in LVEF suggests that further analysis of this association may be warranted.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Patients were queried for adverse events at each clinical visit during the study and at the end-of-study or withdrawal visit. The investigator obtained and recorded on the CRF all observed or volunteered adverse events, the severity (NCT CTCAE v. 3.0) 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 information adequate to determine both the outcome of the adverse event and whether it met the criteria for classification as a serious adverse event. Start and stop dates of adverse events were captured on the CRF.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded by verbatim term, and mapped to appropriate MedDRA terms. Events were graded for severity according to the NCI CTCAE version 3.

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7.1.5.3 Incidence of common adverse events

The adverse event data include data from a single randomized trial in the indicated population. A table summarizing the most common adverse events with a 10% incidence cutoff is contained in section 7.1.5.4.

7.1.5.4 Common adverse event tables

Sponsor's Analysis:

Adverse events occurring in 10% or greater of either treatment arm were reported by the sponsor in Table 28 of the study report (p. 113); these data are presented below (Table 15).

Table 28. Number and Percent of Subjects who Experienced the Most Common (≥ 10% Subjects) Adverse Events by Treatment Arm and Maximum NCI CTCAE Grade Group (AT Population)

	Sunitinib malate (N = 375)		IFN-α (N = 360)	
Preferred Term	Grade 1-2	Grade 3-5	Grade 1-2	Grade 3-5
Any Adverse Events	121 (32.3)	249 (66.4)	166 (46.1)	188 (52.2)
Diarrhea	196 (52.3)	22 (5.9)	71 (19.7)	0 (0.0)
Fatigue	180 (48.0)	35 (9.3)	152 (42.2)	47 (13.1)
Nausea	168 (44.8)	14 (3.7)	129 (35.8)	5 (1.4)
Dysgeusia	160 (42.7)	0 (0.0)	50 (13.9)	0 (0.0)
Anorexia	105 (28.0)	4 (1.1)	96 (26.7)	6 (1.7)
Vomiting	89 (23.7)	15 (4.0)	46 (12.8)	3 (0.8)
Dyspepsia	101 (26.9)	3 (0.8)	14 (3.9)	0 (0.0)
Hypertension	67 (17.9)	34 (9.1)	12 (3.3)	1 (0.3)
Stomatitis	94 (25.1)	3 (0.8)	7 (1.9)	1 (0.3)
Rash	82 (21.9)	3 (0.8)	29 (8.1)	2 (0.6)
Asthenia	52 (13.9)	26 (6.9)	65 (18.1)	20 (5.6)
Palmar-plantar erythrodysesthesia syndrome	58 (15.5)	19 (5.1)	3 (0.8)	0 (0.0)
Mucosal inflammation	70 (18.7)	7 (1.9)	4 (1.1)	1 (0.3)
Headache	65 (17.3)	3 (0.8)	61 (16.9)	0 (0.0)
Back pain	57 (15.2)	11 (2.9)	37 (10.3)	6 (1.7)
Arthralgia	62 (16.5)	4 (1.1)	59 (16.4)	1 (0.3)
Dry skin	63 (16.8)	1 (0.3)	23 (6.4)	0 (0.0)
Pain in extremity	58 (15.5)	5 (1.3)	23 (6.4)	4 (1.1)
Cough	60 (16.0)	2 (0.5)	43 (11.9)	0 (0.0)
Pyrexia	58 (15.5)	3 (0.8)	129 (35.8)	0 (0.0)
Skin discoloration	60 (16.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	33 (8.8)	26 (6.9)	7 (1.9)	0 (0.0)
Constipation	59 (15.7)	0 (0.0)	43 (11.9)	1 (0.3)
Dyspnea	42 (11.2)	15 (4.0)	50 (13.9)	14 (3.9)
Hair color changes	54 (14.4)	0 (0.0)	1 (0.3)	0 (0.0)
Neutropenia	26 (6.9)	26 (6.9)	17 (4.7)	10 (2.8)
Epistaxis	48 (12.8)	4 (1.1)	7 (1.9)	0 (0.0)
Abdominal pain	39 (10.4)	9 (2.4)	23 (6.4)	3 (0.8)
Dry mouth	44 (11.7)	0 (0.0)	25 (6.9)	1 (0.3)
Ejection fraction decreased	35 (9.3)	9 (2.4)	13 (3.6)	4 (1.1)
Anemia	32 (8.5)	11 (2.9)	36 (10.0)	20 (5.6)
Weight decreased	43 (11.5)	0 (0.0)	50 (13.9)	2 (0.6)
Edema peripheral	40 (10.7)	2 (0.5)	13 (3.6)	2 (0.6)
Insomnia	41 (10.9)	1 (0.3)	31 (8.6)	0 (0.0)
Chills	38 (10.1)	3 (0.8)	108 (30.0)	0 (0.0)
Oral pain	38 (10.1)	0 (0.0)	2 (0.6)	0 (0.0)
Decreased appetite	36 (9.6)	2 (0.5)	45 (12.5)	0 (0.0)
Myalgia	30 (8.0)	1 (0.3)	61 (16.9)	2 (0.6)
Dizziness	27 (7.2)	1 (0.3)	38 (10.6)	1 (0.3)
Depression	28 (7.5)	0 (0.0)	38 (10.6)	4 (1.1)

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FDA Analysis:

Table 16 describes adverse events occurring in at least 10% of patients treated with sunitinib.

Table 16--Adverse Events Occurring in ≥ 10% of Patients on the Sunitinib-Treated Arm

	Sunitinib N=375		IFN-α N=360	
Adverse Event, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	370 (99)	250 (67)	354 (98)	184 (51)
Diarrhea	218 (58)	22 (6)	72 (20)	0 (0)
Fatigue	218 (58)	35 (9)	199 (55)	50 (14)
Nausea	183 (49)	16 (4)	136 (38)	5 (1)
Dysgeusia/ageusia	166 (44)	0 (0)	52 (14)	0 (0)
Mucositis/stomatitis*	162 (43)	12 (3)	14 (4)	2 (0.5)
Anorexia/decreased appetite	142 (38)	6 (2)	145 (40)	7 (2)
Bleeding (all sites) Epistaxis	112 (30) 55 (15)	10 (3) 4 (1)	27 (8) 7 (2)	2 (0.6) 0 (0)
Hypertension/blood pressure increased	111 (30)	36 (10)	13 (4)	1 (0.3)
Vomiting	105 (28)	15 (4)	51 (14)	3 (1)
Dyspepsia	105 (28)	4 (1)	14 (4)	0 (0)
Rash	103 (27)	3 (0.8)	40 (11)	2 (0.6)
Thrombocytopenia/decreased platelets	84 (22)	36 (10)	10 (3)	0 (0)
Abdominal pain	83 (22)	10 (3)	44 (12)	5 (1)
Asthenia	79 (21)	27 (7)	85 (24)	20 (6)
Palmar-plantar erythrodysesthesia	78 (21)	20 (5)	3 (0.8)	0 (0)
Skin discoloration/yellow skin	72 (19)	0 (0)	0 (0)	0 (0)
Back pain	70 (19)	13 (3)	44 (12)	6 (2)
Arthralgia	69 (18)	5 (1)	60 (17)	1 (0.3)
Headache	68 (18)	3 (0.8)	61 (17)	0 (0)
Dry skin	67 (18)	1 (0.3)	23 (6)	0 (0)
Pain in extremity/limb discomfort	65 (17)	6 (2)	28 (8)	4 (1)
Cough	64 (18)	2 (0.5)	45 (13)	0 (0)
Neutropenia/decreased neutrophils	63 (17)	39 (10)	38 (11)	8 (2)
Pyrexia	62 (17)	3 (0.8)	129 (36)	0 (0)
Constipation	60 (16)	0 (0)	44 (12)	1 (0.3)
Dyspnea	58 (15)	15 (4)	65 (18)	14 (4)
Hair color changes	56 (15)	0 (0)	1 (0.3)	0 (0)
Anemia/hemoglobin decreased	53 (14)	29 (8)	60 (17)	7 (2)
Dry mouth	45 (12)	0 (0)	26 (7)	1 (0.3)
Weight decreased	45 (12)	0 (0)	54 (15)	2 (0.6)
Ejection fraction decreased	44 (12)	9 (2)	17 (5)	4 (1)

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Edema, peripheral	42 (11)	2 (0.5)	15 (4)	2 (0.6)
Gastroesophageal reflux disease/reflux esophagitis	42 (11)	0 (0)	3 (1)	0 (0)
Chills	42 (11)	3 (0.8)	108 (30)	0 (0)
Insomnia	42 (11)	1 (0.3)	31 (9)	0 (0)
Flatulence	39 (10)	0 (0)	8 (2)	0 (0)
Oral pain	38 (10)	0 (0)	2 (0.6)	0 (0)
Glossodynia	37 (10)	0 (0)	2 (0.6)	0 (0)

* includes mucositis, stomatitis, mucosal inflammation, mouth ulcer, nasal ulcer

7.1.5.5 Identifying common and drug-related adverse events

Based on frequency compared to interferon as well as the previously described safety profile of sunitinib and mechanism of action, the following events are likely drug-related: gastrointestinal events such as diarrhea, nausea, vomiting, dyspepsia, abdominal pain and flatulence; myelosuppressive effects including thrombocytopenia and neutropenia; skin and hair changes including skin discoloration, dry skin, hair color changes and rash; cardiovascular events such as hypertension, decreased left ventricular ejection fraction and peripheral edema; mucositis/stomatitis, oral pain and glossodynia; bleeding events, palmar/plantar erythrodysesthesia and limb/extremity pain or discomfort. Additionally, although the incidence is similar on the two arms, fatigue is likely a drug-related adverse event. Interferon commonly causes fatigue, thus the similarity in incidence when compared to this drug does not rule out a drug related effect.

7.1.6 Less Common Adverse Events

Table 17 describes events occurring in 4-9% of patients treated with sunitinib.

Table 17—Less Common (4-9% Incidence on the Sunitinib Arm) Adverse Events

	Sunitinib N=375		IFN-α N=360	
Adverse Event, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Chest pain/discomfort	35 (9)	2 (1)	24 (7)	4 (1)
Myalgia	33 (9)	1 (0.3)	64 (18)	2 (1)
Alopecia	32 (9)	0 (0)	31 (9)	0 (0)
Pharyngolaryngeal pain	32 (9)	1 (0.3)	7 (2)	0 (0)
Paresthesia	31 (8)	0 (0)	5 (1)	1 (0.3)
Erythema	31 (8)	1 (0.3)	5 (1)	0 (0)
Dehydration	30 (8)	8 (2)	17 (5)	2 (1)
Depression/depressed mood	29 (8)	0 (0)	47 (13)	5 (1)
Dizziness	28 (7)	1 (0.3)	42 (12)	1 (0.3)
Hemorrhoids	27 (7)	0 (0)	3 (1)	0 (0)
Face edema/swelling face	26 (7)	1 (0.3)	1 (0.3)	0 (0)
Nasopharyngitis	26 (7)	0 (0)	4 (1)	0 (0)
Skin exfoliation	26 (7)	1 (0.3)	4 (1)	0 (0)
Neuropathy*	24 (6)	1 (0.3)	12 (3)	1 (0.3)
Shoulder pain	24 (6)	3 (1)	15 (4)	0 (0)
Pleural effusion	19 (5)	5 (1)	3 (1)	3 (1)
Lacrimation increased	19 (5)	0 (0)	0 (0)	0 (0)
Visual disturbance**	17 (5)	0 (0)	9 (3)	0 (0)
Dysphonia	17 (5)	0 (0)	3 (1)	0 (0)
Chromaturia	16 (4)	0 (0)	1 (0.3)	0 (0)
Dysphagia	16 (4)	4 (1)	3 (1)	0 (0)
Flank pain	15 (4)	0 (0)	9 (3)	0 (0)
Confusional state	14 (4)	7 (2)	9 (3)	0 (0)
Nasal congestion	14 (4)	0 (0)	7 (2)	0 (0)

* includes the term "neuropathy", and peripheral neuropathies (both sensory and motor)
**also includes vision blurred and visual acuity reduced

Other less common AEs of interest:

Endocrine: In nonclinical studies, thyroid and adrenal glands were identified as target organs of toxicity for sunitinib.

Hypothyroidism was reported in 11 patients (3%) treated with sunitinib (including one grade 3) vs. 1 patient (0.3%) treated with IFN- α.

The potential for adrenal toxicity in humans was evaluated prior to initial NDA submission and is reviewed under NDA 21-968. In the current study, no patients treated with sunitinib and one patient treated with IFN- α was reported to have treatment-emergent adrenal insufficiency.

Pancreatitis:

Increases in amylase and lipase are commonly seen in patients treated with sunitinib. Therefore, the number of patients with pancreatitis reported as an AE was analyzed. There were 5 patients (1.3%) with pancreatitis reported in the sunitinib group (one grade 3) and one patient (0.3%) with pancreatitis in the IFN- α group.

Fungal Infections:

Eleven patients (3%) treated with sunitinib developed fungal infections, while no patients treated with IFN- α were reported to have fungal infections. For those patients in whom a location was specified, all were superficial (groin, mouth). One fungal infection was reported as "widespread"; this was the only grade 3 event in this category. There were no reports of fungemia or fungal pneumonia.

Herpetic infections:

Herpes simplex infections were reported in 11 patients (3%) treated with sunitinib and one patient treated with IFN- α (0.3%). Herpes zoster infections were reported in 3 patients (0.8%) treated with sunitinib and no patients treated with IFN- α. All infections were grade 1/2.

Renal failure/insufficiency:

Nine patients (2.4%) treated with sunitinib vs. three patients (0.8%) treated with IFN had renal insufficiency or failure reported as AEs. Worst grade was 3/4 in 3 sunitinib patients and 2 IFN- α patients.

Thromboses:
On the sunitinib arm, four patients (1%) experienced deep venous thrombosis (DVT), and four (1%) developed pulmonary embolism (PE). On the interferon arm, one patient (0.3%) developed DVT and four developed PE (1%).

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Hematology (including red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelet count and white blood cell count and differential) and chemistry (including total and direct bilirubin, ALT, AST, alkaline phosphatase, LDH, CK, amylase, lipase, total protein, albumin, globulin, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, BUN, creatinine, uric acid and glucose) parameters were evaluated at baseline, cycle 1 days 14 and 28, and cycles 2-4 day 1 and 28. For subsequent cycles, hematology labs were drawn on days 1 and 28 and chemistries were on day 1 only. Both chemistry and hematology labs were performed at end-of-study or withdrawal, and during post-treatment follow-up as necessary for unresolved adverse events.

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

Laboratory data from the randomized, IFN- α controlled trial A6181034 were evaluated. There are no placebo controlled laboratory data in patients with renal cell carcinoma.

7.1.7.3 Standard analyses and explorations of laboratory data

Hematology Abnormalities

Grade 3/4 neutropenia, leucopenia and thrombocytopenia were more common in patients receiving sunitinib, while anemia and lymphopenia were more commonly observed in IFN- α patients.

Sponsor's analysis:

Patients experiencing treatment-emergent grade 3 and 4 hematology abnormalities were reported by the sponsor in the clinical study report Table 33 (p. 127), shown below in Table 18..

Table 18—Hematologic Abnormalities (Sponsor's Analysis)

Number and Percent of Subjects with Shifts from Grade ≤ 2 at Baseline to Grade ≥ 3 Post-Baseline for Hematology Variables in All Cycles Combined (AT Population)

Variable	Sunitinib malate (N = 375)	IFN-α (N = 360)
ANC	43 (11.5)	24 (6.7)
Hemoglobin	11 (2.9)	15 (4.2)
Lymphocytes	40 (10.7)	73 (20.3)
Platelets	29 (7.7)	0 (0.0)
WBC	18 (4.8)	8 (2.2)

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FDA Analysis:
This analysis includes patients with grade 3/4 abnormalities on study, regardless of missing baseline assessments, is presented in Table 19.

Table 19--Treatment-Emergent Grade 3/4 Hematologic Abnormalities

	Sunitinib n=375		IFN-α n=360	
Laboratory Parameter, n (%)	Grade 3/4	Grade 4	Grade 3/4	Grade 4
Granulocytes	44 (12)	3 (0.8)	24 (7)	0 (0)
Lymphocytes	41 (11)	4 (1)	77 (21)	6 (2)
Platelets	30 (8)	2 (0.5)	0 (0)	0 (0)
Total white blood cells	19 (5)	0 (0)	8 (2)	0 (0)
Hemoglobin	11 (3)	1 (0.2)	16 (4)	2 (0.6)

Creatinine:
Thirty-seven percent of patients on both arms had a creatinine value above the upper limit of normal at screening. One patient on each arm had a grade 3/4 increase in creatinine on study. However, smaller increases in creatinine were more common. Creatinine values of ≥ 2 mg/dl in patients with a baseline value of < 2 mg/dl occurred in 35 sunitinib-treated patients (9%) and 21 IFN- α patients (6%). Of these, 30 of the sunitinib patients and 17 IFN- α patients had a baseline creatinine that was above the upper limit of normal (but less than 2 mg/dl).

Amylase/lipase:
Treatment-emergent grade 3/4 changes in amylase occurred in 16 sunitinib-treated patients (4%) and six IFN- α patients (2%); Treatment-emergent grade 3/4 changes in lipase occurred in 57 sunitinib-treated patients (15%) and 19 IFN- α patients (5%). Pancreatitis as an adverse event was less common (see 7.1.6).

Bilirubin:
Total bilirubin was elevated to grade 3 in 3 sunitinib patients (1%) and no IFN- α patients. All 3 subsequently recovered to normal. This elevation was largely due to increases in indirect bilirubin. None of the patients had a history of liver metastases; one had a mildly abnormal bilirubin at baseline. Alkaline phosphatase was normal in all cases. AST/ALT were also normal in two of the cases, they were mildly abnormal in one case. All three patients had an isolated grade 3 abnormality, but lesser abnormalities were noted in other cycles. Bilirubin values tended to be highest on day 28 of a cycle (the last day of dosing), and lower on day 1 of the following cycle (following a two week rest period).

Sodium:
Grade 3/4 treatment-emergent hyponatremia occurred in 19 patients receiving sunitinib (5%) vs. 8 patients receiving IFN- α (2%). Hypernatremia was less common (one sunitinib patient and two IFN- α patients).

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Potassium:
Hyperkalemia grade 3/4 occurred in 10 sunitinib-treated patients (3%) and 15 IFN patients (4%). Hypokalemia grade 3 occurred in two patients (one sunitinib, one IFN).

AST:
Six patients on each arm had grade 3/4 treatment-emergent increases in AST. Five of the six had normal baseline AST and either a single isolated abnormal AST or 2 non-sequential abnormal values with the remaining AST measurements normal. A single patient treated with IFN had a mildly abnormal baseline AST and several grade 3 abnormalities on study.

ALT:
Ten sunitinib patients (3%) and six IFN- α patients (2%) experienced treatment-emergent grade 3/4 elevations in ALT. Many of these patients had multiple abnormal values on study (with one or two reaching grade 3 or 4 toxicity). A single patient (pt 324) experienced grade 4 ALT. This was a sunitinib treated patient with a normal baseline ALT which rose to 1020 in the first cycle. This was the last laboratory value available for this patient, who was subsequently withdrawn from the study due to lack of efficacy.

Uric acid:
Thirty-eight patients on the sunitinib arm (10%) vs. 16 on the IFN- α arm (4%) had treatment-emergent grade 4 elevations in uric acid (there were no grade 3 elevations).

Alkaline phosphatase:
Grade 3/4 elevations occurred in 6 (1.6%) sunitinib vs. 4 IFN- α patients (1.1%).

Glucose:
Hyperglycemia (grade 3) occurred in 8 sunitinib (2%) vs. 17 IFN- α patients (5%).

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including pulse, blood pressure, temperature and respiratory rate, were evaluated in each patient at baseline, days 1 and 28 of each cycle and at end of study or withdrawal.

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

Vital signs were evaluated in the IFN controlled study A6181034.

7.1.8.3 Standard analyses and explorations of vital signs data

Hypertension is a commonly reported adverse reaction in patients receiving sunitinib. Patients who experience severe elevations in blood pressure are of particular concern due to the increased likelihood of end-organ damage. The vital signs data was therefore evaluated for patients experiencing the most severe elevations in blood pressure, defined here as a systolic blood pressure (sbp) of >200 mm Hg and/or a diastolic blood pressure (dbp) of > 110 mm Hg.

Twenty patients on sunitinib (5%) vs. two patients (0.5%) on IFN experienced severe elevations in blood pressure meeting the above criteria. Of the twenty sunitinib patients, 17 had elevations in dbp to > 110 mm Hg, with only on of these patients also reported as having an sbp > 200 mm Hg. The remaining three patients had sbp > 200 mm Hg without an increase in dbp > 110 mm Hg, but two those had dbp of > 100 mm Hg. Only one patient (pt. 162) met these criteria at more than one visit while on study.

Eighteen on the twenty sunitinib patients were on anti-hypertensive medications during the study. Nine of these patients were on anti-hypertensives at baseline (including two who started them immediately before beginning study therapy). Of those, seven had additional anti-hypertensive medications added on study. Eleven patients were not on anti-hypertensive drugs at baseline but began them on study.

The incidence of bradycardia on study was also evaluated. Twenty-seven patients had a pulse of < 50 at some point on study, including 21 (6%) on the sunitinib arm and six (2%) on the IFN arm. Of these, four sunitinib patients and one IFN patient also had bradycardia at baseline; the incidence of treatment-emergent bradycardia was 5% (17/375) on the sunitinib arm and 1% (5/360) on the IFN arm.

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 IC_{50} of 266 nM and 4100 nM, respectively. *In vivo*, corrected QT was increased by 20-50 msec in monkeys.

On the phase 3 study (A6181034), ECGs were obtained at baseline and day 28 in patients on both the sunitinib and IFN arms of the study.

A thorough QT study was also submitted and was reviewed by the Interdisciplinary Review Team (IRT) for the review of Thorough QT Studies. Study A6181005 was designed to assess

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the effects of high peak plasma concentrations of sunitinib + SU012662 on the QTc interval in subjects with advanced solid tumors. The positive control was moxifloxacin.

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

QTc was evaluated in both the phase 3 study and in a thorough QT study (A6181005). Data from the MRCC study was reviewed by the DDOP Medical Reviewer and the IRT-TQT; data from the TQT study were reviewed primarily by the IRT-TQT.

7.1.9.3 Standard analyses and explorations of ECG data

A6181034:
Triplicate ECGs were performed at baseline, on day 28 of cycle 1 and when clinically indicated thereafter. Change from baseline to day 28 is summarized in Table 20.

Table 20--Change in QTcF on Study A6181034

	Sunitinib N=375	IFN-α N=360
Change from baseline in QTcF, mean (msec)	8	3.8
Standard deviation (range)	23.7 (-95.4 to 117.3)	24.2 (-85.6 to 116.3)

Eleven sunitinib treated patients (2.9%) and 8 IFN treated patients (2.2%) had CTCAE grade 2 changes in QTc (> 470-500 msec or a change in QT of > 60 msec). One sunitinib patient and no IFN-α patients had a QTC of > 500 msec (grade 3). There was one report in a sunitinib-treated patient of grade 4 QT prolongation listed as an adverse event; the event resolved after treatment discontinuation. There is no corresponding ECG record of the QT interval at the time of the event.

A6181005:

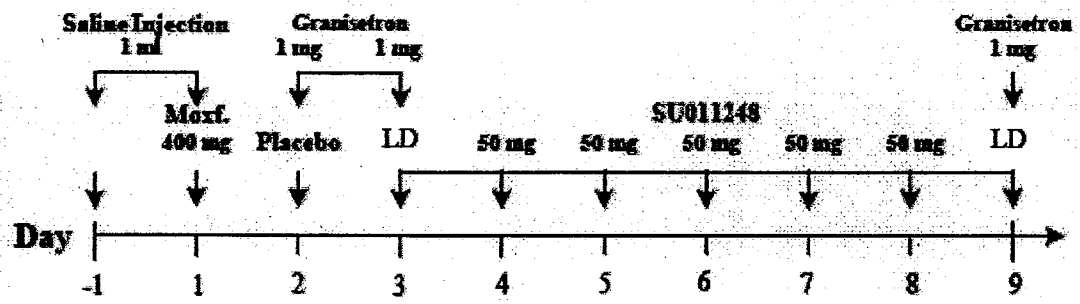
This study was reviewed by the IRT-TQT. A summary of the study design and review conclusions are presented here.

This study was a single-blind study in patients with advanced solid tumors. Patients underwent serial electrocardiogram (ECG) assessments on Day -1, then received a single dose of moxifloxacin on Day 1 and a single dose of placebo on Day 2, followed by a 1-week course of SU011248 (loading dose (LD) on Days 3 and 9, maintenance dose on Days 4-8). In order to minimize the probability of inducing nausea and or vomiting, all subjects were pretreated with intravenous granisetron (1 mg) prior to dosing on Days 3 and 9. Granisetron was also administered to subjects on Day 2 (placebo only day) in order to assess its effect on ECG. Two loading dose levels were evaluated in this study. The first group received 150 mg as the loading

dose on day 3 and day 9, and the second group received 200 mg loading doses on days 3 and 9. Both groups received 50 mg maintenance doses on days 4, 5, 6, 7 and 8.

The study design is displayed in Figure 6.

Figure 6: Schematic of Study A6181005 Study Design



(Reproduced from Sponsor, Figure SI, page 3)

ECGs were recorded in triplicate at the time points described in Table 21.

Table 21—Highlights of Schedule of Interventions

Study Day	-1	1	2	3	4-8	9
Intervention	Baseline	Moxifloxacin 400 mg	Placebo	Loading dose 150 or 200 mg	Daily dose: 50 mg	Loading dose: 150 or 200 mg
12-Lead ECGs	Record ECGs#	Record ECGs#	Record ECGs#	Record ECGs#	Not collected	Record ECGs#
PK Samples	Not collected	Not collected	Not collected	Collected##	Not collected	Collected##
Meal Instructions	Standard###	Standard###	Standard###	Standard###	Standard###	Standard###

predose (x3), 2, 4, 6, 8, 12, 16 and 24 hrs postdose
predose (0 hr), and 3, 4, 7, 9, 12 and 24 hr post-dose. Two additional blood samples collected at 72 and 168 hours post Day 9 dose.
Standardized meals given after dose administration, at 4 hrs and 9 hrs after dosing. Light snack given at 7 and 12 hrs after dosing.
(Derived from Sponsor, Table 1, page 67)

Results (IRT-QT):

Table 21 (Table 8 of the IRT report) displays a summary of the results for maximum mean changes from baseline in QTc following sunitinib on day 3 and day 9.

An effect on QTc (defined as a mean placebo-adjusted change of ≥ 10 msec with a 90% CI upper limit ≥ 15 msec) was observed on Day 3 using the within-day baseline correction method, and on

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Day 9 using both baseline correction methods (see table above). The maximum mean placebo adjusted change from (time-matched) baseline QTcF was 14.5 msec (90% CI: 9.5 – 19.5) at therapeutic levels of sunitinib (day 3) and was 20.3 msec (90% CI: 13.4 – 27.1) at supra-therapeutic (2-fold higher than therapeutic) levels of sunitinib.

Table 21—Changes in QTcF on Study A6181005 (IRT Report)

Table 8. Summary of Maximum Mean Placebo-Adjusted Changes from Baseline in QTcF and QTcS Following Dosing with Sunitinib – Day 3 and Day 9 – All Patients Combined (Evaluable and IT Populations).

Parameter	Population	Baseline Correction Method	N	Time (hr)	Maximum Mean Placebo-Adjusted Change from Baseline *	90% CI *
Day 3						
QTcF (msec)	Evaluable	Within-day	24	24	14.5	9.5, 19.5
QTcF (msec)	Evaluable	Time-matched	24	24	9.6	4.1, 15.1
QTcF (msec)	ITT	Within-day	47	24	11.9	8.6, 15.2
QTcF (msec)	ITT	Time-matched	47	24	6.9	3.3, 10.4
QTcS (msec)	Evaluable	Within-day	24	24	12.7	8.1, 17.3
QTcS (msec)	Evaluable	Time-matched	24	24	7.4	2.4, 12.5
Day 9						
QTcF (msec)	Evaluable	Within-day	24	24	20.3	13.4, 27.1
QTcF (msec)	Evaluable	Time-matched	24	24	15.4	8.4, 22.4
QTcF (msec)	ITT	Within-day	43	24	17.7	12.9, 22.6
QTcF (msec)	ITT	Time-matched	43	24	12.7	8.1, 17.3
QTcS (msec)	Evaluable	Within-day	24	24	19.2	12.3, 26.1
QTcS (msec)	Evaluable	Time-matched	24	24	13.9	7.0, 20.9

(Reproduced from Sponsor, Table 12, page 115)

IRT-TQT recommended changes to the labeling based on TQT results;

In the HIGHLIGHTS Section:
WARNINGS AND PRECAUTIONS

- Prolonged QTc intervals occurred at therapeutic concentrations. Torsade de Pointes has been observed in <0.1% of patients. Use with caution in patients at higher risk for developing QT interval prolongation. When using SUTENT, the prescriber should consider periodic monitoring of on-treatment electrocardiograms. (5.3)

In the Full Prescribing Information:

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Under WARNINGS AND PRECAUTIONS SECTION:
5.3 QT Interval Prolongation

QT interval prolongation was investigated in a trial with 24 evaluable patients, aged 20-87 years, with advanced malignancies. At therapeutic plasma concentrations, the maximum QTcF (Fridericia's Correction) mean change from (within-day) baseline was 14.5 msec (90% CI: 9.5 - 19.5 msec). At approximately twice therapeutic concentrations, the maximum QTcF mean change from (within-day) baseline was 20.3 msec (90% CI: 13.4 – 27.1 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 QTc >500 msec (Grade 2, CTCAE v.3.0). No patient in this study presented with a cardiac arrhythmia.

At therapeutic plasma concentrations, SUTENT has been shown to prolong the QTcF interval, which QT interval prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT exposed patients. SUTENT should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, the prescriber should consider periodic monitoring of on treatment electrocardiograms and electrolytes. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered.

There are no new data for sections 7.1.10 to 7.1.16; the information provided below was excerpted from the initial NDA review of 21-968.

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. Embryolethality and developmental abnormalities were observed in rats at the dose of 5 mg/kg/day. In rabbits, embryolethality 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 non-clinical 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 have been performed in a pediatric population.

7.1.16 Overdose Experience

No overdose of sunitinib was reported in completed clinical studies.

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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

No new safety issues have been identified based on the post-marketing experience.

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

The safety evaluation relied on data from a single, randomized trial of 750 patients with metastatic renal cell carcinoma, who were randomized 1:1 to receive either sunitinib or IFN-α (375 patients per arm). The major weakness of this study in evaluating safety is the lack of placebo controlled data; there are no placebo controlled trials for sunitinib in renal cell carcinoma, although a placebo controlled trial was performed in patients with gastrointestinal stromal tumors.

7.2.1.2 Demographics

The demographics of the treated population adequately represent the demographics of patients with this disease.

7.2.1.3 Extent of exposure (dose/duration)

The median duration of treatment for patients on the sunitinib arm was 5.6 months (median 169 days, min 13 days/ max 469 days), with a median number of cycles started of 4 (min 1, max 11). The median duration of treatment for patients on the IFN-α arm was 4.1 months (median 123.5 days, min 4 days/ max 410 days), with a median number of cycles started of 3 (min 1, max 10).

Average (mean) daily dose administered was 47.7 mg for sunitinib (median = 50 mg) and 7.6 MU for IFN- α (median= 8.2 MU). The median relative dose intensity [(total dose administered/total dose assigned)* 100] was 100% in both arms, however, the mean relative dose intensity was 97.1% vs. 95.9% in the sunitinib vs. IFN- α arms, respectively.

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7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

Three hundred and seventy five patients with metastatic renal cell carcinoma were treated with sunitinib on study A6181034. An additional 169 patients with MRCC were treated on the two single-arm trials which served as the basis for the accelerated approval of sunitinib in January 2006. Thus, across the three studies, safety data from 544 patients with MRCC have been reviewed. While there is no placebo controlled data for the MRCC patient population, such data are available in the GIST indication (202 patients were treated with sunitinib and 102 with placebo in that study).

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 evaluated with the original NDA submission and 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 evaluation for potential adverse events was adequate. The clinical significance of the observed changes in left ventricular ejection fraction is currently being performed as a sub-study of an NCI-sponsored, placebo controlled trial in the adjuvant treatment of renal cell carcinoma.

7.2.8 Assessment of Quality and Completeness of Data

The databases evaluated in the safety review were complete and of good quality.

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

Common drug-related adverse events included GI events [diarrhea (58% sunitinib vs. 20% IFN)), nausea (49% vs. 38%), mucositis (43% vs. 4%), vomiting (28% vs. 14%), dyspepsia (28% vs. 4%), abdominal pain (22% vs. 12%), gastroesophageal reflux (11% vs. 1%), oral pain (10% vs. 1%), glossodynia (10% vs. 1%) and flatulence (10% vs. 2%)], bleeding (30% vs. 8%), hypertension (30% vs. 4%), dermatologic events [rash (27% vs. 11%), skin discoloration (19% vs. 0%), dry skin (18% vs. 6%), and hair color changes (15% vs. <1%)], palmar-plantar erythrodysesthesia (21% vs. 1%), limb pain (17% vs. 8%), decreases in cardiac ejection fraction (12% vs. 5%), and peripheral edema (11% vs. 4%). Although the incidence of fatigue is not higher in patients treated with sunitinib, the similarity in incidence of fatigue to patients treated with IFN (58% vs. 55%), a well known cause of fatigue, makes it likely that fatigue is also related to sunitinib.

Grade 3/4 adverse events more common on the sunitinib arm included hypertension (10% vs. <1%), diarrhea (6% vs. 0%), palmar-plantar erythrodysesthesia (5% vs. 0%), nausea (4% vs. 1%), vomiting (4% vs. 1%), mucositis (3% vs. 1%), and bleeding (3% vs. 1%).
Less common adverse events that are likely drug related include pharyngeolaryngeal pain (9% vs 2%), paresthesias (8% vs. 1%), erythema (8% vs. 1%), hemorrhoids (7% vs. 1%), facial edema (7% vs. 1%), nasopharyngitis (7% vs. 1%), skin exfoliation (7% vs. 1%), neuropathy (6% vs. 3%), pleural effusion (5% vs. 1%), lacrimation increased (5% vs. 0%), dysphonia (5% vs. 1%), chromaturia (4% vs. <1%), dysphagia (4% vs. 1%), and hypothyroidism (3% vs. <1%).

Patients receiving sunitinib were more likely to develop significant changes in LVEF and/or clinical evidence of ventricular dysfunction. Thirteen patients on sunitinib (4%) and four on IFN-α (1%) experienced declines in LVEF of > 20% from baseline and to below 50%. One patient who received sunitinib was diagnosed with congestive heart failure and three patients were diagnosed with left ventricular dysfunction.

Grade 3/4 laboratory abnormalities which are more common in sunitinib-treated patients include hematologic abnormalities [neutropenia (12% vs. 7%), thrombocytopenia (8% vs. 0%), and leucopenia (5% vs. 2%)], increased lipase (15% vs. 5%), increased amylase (4% vs. 2%), hyponatremia (5% vs. 2%), hyperuricemia (10% vs. 4%) and hyperbilirubinemia (1% vs. 0%).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.2 Explorations for Predictive Factors

Not applicable.

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7.4.3 Causality Determination

Causality determination was based on the following factors:

- Incidence of the event compared to control
- Knowledge about the drug's safety profile based on the adverse reaction data from the placebo controlled GIST study and prior MRCC studies
- Plausibility based on the drug's mechanism of action (MOA), and known toxicities of agents with similar MOA
- Preclinical toxicology results

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 / mg daily on the 4/2 schedule are appropriate in the setting of intolerable toxicity.

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8.2 Drug-Drug Interactions

No new data regarding drug-drug interactions were provided.

8.3 Special Populations

A hepatic impairment study was submitted and reviewed by the clinical pharmacology review team. Patients with mild to moderate hepatic dysfunction were studied and did not have significantly different exposure to sunitinib compared to patients with normal hepatic function. The following statement was added to the labeling:

"Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN. No dose adjustment is required when administering SUTENT to patients with Child Pugh Class A or B hepatic impairment."

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8.4 Pediatrics

To date, sunitinib has not been studied in pediatric patients. A proposed pediatric study request was submitted by the sponsor to the IND on July 1, 2005 and a formal Written Request was made by FDA on October 6, 2006. A pediatric protocol was submitted to the IND on November 22, 2006, entitled "A Phase 1 Study of Sunitinib (SU11248), an Oral Multi-Targeted Tyrosine Kinase Inhibitor, in Children with Refractory Solid Tumors".

This dose-escalation study will be performed in pediatric patients aged 2-21 years with refractory solid tumors for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

Plans for further clinical development in pediatric patients have been described by the sponsor as follows.

"The first Phase 2 study would be conducted in pediatric patients with GIST since efficacy has been demonstrated in adult patients with this disease. GIST tumors in pediatric patients are driven by KIT and PDGFR, which lead to tumor formation just as in adult patients. There is strong scientific rationale to evaluate patients with anaplastic astrocytoma and glioblastoma multiform since these tumors tend to over express PDGFR and are highly vascular tumors that may respond to agents that inhibit angiogenesis. _____

_____ 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."

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8.5 Advisory Committee Meeting

No advisory committee meeting was held to discuss this application.

8.6 Literature Review

No additional information regarding the efficacy or safety of sunitinib was obtained via literature review.

8.7 Postmarketing Risk Management Plan

There have been no changes to the postmarketing risk management plan.

8.8 Other Relevant Materials

Not applicable.

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9 OVERALL ASSESSMENT

9.1 Conclusions

Study A6181034 is a randomized, open label trial in patients with treatment-naïve metastatic renal cell carcinoma. Seven hundred and fifty patients were randomized 1:1 to receive either sunitinib or IFN-α. Sunitinib was given at a starting dose of 50 mg orally once daily for 4 weeks, followed by a two week rest period (4/2 schedule). IFN-α was given subcutaneously on three nonconsecutive days per week at a starting dose of 3 MU per dose during the first week, 6 MU per dose the second week and 9 MU per dose thereafter.

Three hundred and seventy-five patients were randomized to each arm. The two treatment arms were well balanced for baseline demographic characteristics, including age, gender, and race. Patients were required to have some component of clear cell histology and most (90%) had undergone prior nephrectomy. The median number of sites of disease was two: common sites included lung, lymph nodes, bone and liver.

For the primary analysis of PFS in the ITT population based on independent review data, there were 96 events (25.6%) of progression or death on the sunitinib arm compared with 154 events (41.1%) of progression or death on the IFN arm. Median PFS was 47.3 weeks (95% CI 42.6, 50.7) for sunitinib-treated patients and 22.0 weeks (95% CI 16.4, 24.0) for patients treated with IFN; the hazard ratio was 0.415 (95% CI .320, 0.539, $p<0.000001$). These results were supported by three sensitivity analyses of PFS. Overall survival data were not mature at the time of the second interim analysis.

Overall response rate was also improved on the sunitinib arm compared to the IFN arm, with an ORR of 27.5% (95% CI 23.0%, 32.3%) vs. 5.3% (95% CI 3.3%, 8.1%). The response rate noted on the sunitinib arm is similar to the response rates seen in two single-arm trials of sunitinib in patients with cytokine-refractory MRCC.

The updated response data from study A6181006 include an ORR (all partial responses) of 34% (95% CI 25.0, 43.8) as evaluated by the core radiology laboratory, which was the protocol-specified primary analysis. Duration of response data are not mature (the median has not been reached with nine failures and 27 censored patients); the lower bound of the 95% CI was reported as 42 weeks.

Common drug-related adverse events included GI events [diarrhea (58% sunitinib vs. 20% IFN)), nausea (49% vs. 38%), mucositis (43% vs. 4%), vomiting (28% vs. 14%), dyspepsia (28% vs. 4%), abdominal pain (22% vs. 12%), gastroesophageal reflux (11% vs. 1%), oral pain (10% vs. 1%), glossodynia (10% vs. 1%) and flatulence (10% vs. 2%)], bleeding (30% vs. 8%), hypertension (30% vs. 4%), dermatologic events [rash (27% vs. 11%), skin discoloration (19% vs. 0%), dry skin (18% vs. 6%), and hair color changes (15% vs. <1%)], palmar-plantar erythrodysesthesia (21% vs. 1%), limb pain (17% vs. 8%), decreases in cardiac ejection fraction (12% vs. 5%), and peripheral edema (11% vs. 4%). Although the incidence of fatigue is not

higher in patients treated with sunitinib, the similarity in incidence of fatigue to patients treated with IFN (58% vs. 55%), a well known cause of fatigue, makes it likely that fatigue is also related to sunitinib.

Grade 3/4 adverse events more common on the sunitinib arm included hypertension (10% vs. <1%), diarrhea (6% vs. 0%), palmar-plantar erythrodysesthesia (5% vs. 0%), nausea (4% vs. 1%), vomiting (4% vs. 1%), mucositis (3% vs. 1%), and bleeding (3% vs. 1%).

Less common adverse events that are likely drug related include pharyngeolaryngeal pain (9% vs 2%), paresthesias (8% vs. 1%), erythema (8% vs. 1%), hemorrhoids (7% vs. 1%), facial edema (7% vs. 1%), nasopharyngitis (7% vs. 1%), skin exfoliation (7% vs. 1%), neuropathy (6% vs. 3%), pleural effusion (5% vs. 1%), lacrimation increased (5% vs. 0%), dysphonia (5% vs. 1%), chromaturia (4% vs. <1%), dysphagia (4% vs. 1%), and hypothyroidism (3% vs. <1%).

Patients receiving sunitinib were more likely to develop significant changes in LVEF and/or clinical evidence of ventricular dysfunction. Thirteen patients on sunitinib (4%) and four on IFN-α (1%) experienced declines in LVEF of > 20% from baseline and to below 50%. One patient who received sunitinib was diagnosed with congestive heart failure and three patients were diagnosed with left ventricular dysfunction.

Grade 3/4 laboratory abnormalities which are more common in sunitinib-treated patients include hematologic abnormalities [neutropenia (12% vs. 7%), thrombocytopenia (8% vs. 0%), and leucopenia (5% vs. 2%)], increased lipase (15% vs. 5%), increased amylase (4% vs. 2%), hyponatremia (5% vs. 2%), hyperuricemia (10% vs. 4%) and hyperbilirubinemia (1% vs. 0%).

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 conversion of this application for sunitinib for the treatment of advanced renal cell carcinoma (RCC) to regular approval. This recommendation is based on a clinically and statistically robust improvement in progression-free survival in patients receiving sunitinib as first-line treatment of metastatic renal cell carcinoma (MRCC) compared to those patients receiving interferon-α (IFN- α).

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

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hypertension, bleeding, changes in left ventricular ejection fraction and dermatologic effects, will be described in the labeling.

9.3.2 Required Phase 4 Commitments

There is one remaining outstanding required phase 4 commitment from the initial NDA approval:

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

FDA, Pfizer and NCI (the sponsor of this ECOG study) have discussed and implemented a sub-study design to further characterize changes in left ventricular ejection fraction in patients receiving sunitinib compared to those receiving placebo. It is anticipated that data from this sub-study will be available in 2011.

Additionally, one prior commitment, to provide efficacy data from study A6181034 has been partially fulfilled. The commitment required data including PFS, ORR, duration of response and OS to be submitted. While ORR and PFS data have been submitted, duration of response and OS data were not mature. The submission of these data, when mature, will be the subject of an additional PMC.

- The sponsor will submit the complete study report and datasets with the final statistical analysis of overall survival and duration of response for study A6181034.

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

Major changes to the labeling included:

- Conversion to PLR format
- Adding safety and efficacy data obtained from study A6181034
- Updating the data on QT prolongation and torsade de pointes
- Adding data obtained from the hepatic impairment study

9.5 Comments to Applicant

None.

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/s/

Vicki Goodman
1/30/2007 04:44:58 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	21-968/S003/S004/S005
Drug Name:	Sunitinib malate (Sutent, SU011248)
Applicant:	Pfizer
Indication(s):	Treatment of Patients with Advanced Renal Cell Carcinoma
Date(s):	Submission Date: March 31, 2006 for No. 003/004 August 9, 2006 for No. 005 PDUFA Date: February 11, 2007 Review Completion Date:
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Shenghui Tang, Ph.D.
Concurring Reviewer:	Rajeshwari Sridhara, Ph.D., Team Leader Aloka Chakravarty, Ph.D., Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Vicki Goodman, M.D., Amna Ibrahim, M.D.
Project Manager:	Ms. Christry Cottrell
Keywords:	Progression-Free Survival, Objective response rate, Duration of response, time to tumor progression, Overall Survival

Table of Contents

1 Executive Summary

1.1 Conclusions and Recommendations

On 10 August 2005, the sponsor submitted an application to evaluate the efficacy of single-agent SU011248 (Sunitinib, SUTENT®) in patients with progressive metastatic renal cell carcinoma who were refractory to 1 prior cytokine therapy (IFN, IL-2, or IFN + IL-2). The application was for accelerated approval and the primary efficacy endpoint was the objective response rate (ORR). It was based primarily on data from the Phase II pivotal study, A6181006. Supportive data were provided from the Phase II study (RTKC-0511-014) in the same patient population. The FDA granted accelerated approval for Sunitinib (SUTENT®) on 26 January 2006 for advanced renal cell carcinoma (RCC).

For the purpose of converting the accelerated approval to a regular approval, the sponsor submitted efficacy and safety data from a confirmatory Study A6181034, "A Phase 3, Randomized Study of SU011248 versus Interferon-α (IFN-α) as First Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma". The submission No. 003 included an interim analysis for ORR and the submission No. 005 included an interim analysis for Progression-Free Survival (PFS).

Primary efficacy analysis of Study A6181034 is PFS analysis for the ITT population as assessed by the independent imaging core laboratory. At the time of data cutoff for the interim PFS analysis (15 November 2005), 750 subjects were randomized: 375 in the Sunitinib arm and 375 in the IFN-α arm. The PFS analysis included 96 events (25.6%) for PFS in the Sunitinib arm and 154 events (41.1%) for PFS in the IFN-α arm. Estimated medians of PFS in the Sunitinib arm and the IFN-α arm were 47.3 weeks and 22.0 weeks respectively. The hazard ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm, was 0.415 (p-value < 0.000001).

At the time of PFS analysis, the analysis for the ORR based on the core imaging laboratory results identified 103 (27.5%) versus 20 (5.3%) partial responses on Sunitinib versus IFN-α, respectively; of these subjects, 16 (15.5% subjects with responses) vs. 0 (0.0% subjects with responses) subsequently progressed or died. Median duration of response (DR) was 40.9 weeks (95% CI: 30. 1 to 54.1 weeks) on Sunitinib. Duration of response on IFN-α could not be calculated because no subjects had subsequent progression or death.

The submitted data support the claim based on PFS analysis. Whether the endpoint and the size of the effect on the primary endpoint in Study A6181034 are adequate for converting the accelerated approval to a regular approval is deferred to clinical judgment.

1.2 Brief Overview of Clinical Studies

Study A6181034 is a randomized, multi-center, international, phase 3 study evaluating the efficacy and safety of single-agent Sunitinib compared to IFN-α in patients with treatment-naïve MRCC. Patients are randomized 1:1 to the treatment arms. Patients received treatment with either Sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily administration followed by 2 weeks of rest (Schedule 4/2), or IFN-α, administered as a subcutaneous injection on 3 non-consecutive days each week.

1.3 Statistical Issues and Findings

For the purpose of converting the accelerated approval to a regular approval, the sponsor submitted efficacy and safety data from Study A6181034, "A Phase 3, Randomized Study of Sunitinib versus Interferon-α (IFN-α) as First Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

Statistical Issues:

According to the protocol, PFS data were censored on the day following the date of the last on-treatment (including 28 day follow-up period) tumor assessment documenting absence of PD for subjects who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment or were removed from treatment prior to documentation of objective tumor progression. It was shown in the PFS analysis that the lack of radiographic monitoring of patients after the 28 day follow-up caused a convergence of two PFS curves at about 48 to 50 weeks.

The lack of radiographic monitoring of patients after the 28 day follow-up was also the reason for the convergence of two time-to-progression (TTP) curves at about 48 to 50 weeks.

The second interim analysis was for PFS analysis which was planed when approximately 354 events have occurred (approximately 75% of the total number of events expected). As of the data cutoff date (15 November 2005) for the interim PFS analysis, 750 subjects had been randomized in Study A6181034; these 750 subjects comprised the ITT population. Three hundred seventy-five subjects were randomized to the Sunitinib arm, and 375 were randomized to the IFN-α arm. Two hundred fifty PFS events were independently confirmed. Assuming a 2-sided test with the observed number of events (250), accounting for the one prior ORR interim analysis that occurred after 83 PFS events had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the lower

limit of the log-rank statistic that would indicate stopping for efficacy would be 2.875 and the nominal significant level was 0.0042. The observed log-rank statistic was 6.8524 and the observed p-value was less than 0.000001.

Because the data were not yet mature, median OS had not been achieved on either treatment arm. The hazard ratio for OS was 0.650 (95% CI: 0.449 to 0.942; p = 0.0219); which was not statistically significant based on the stopping boundaries for this interim analysis. Accounting for the one prior ORR interim analysis that occurred after 29 deaths had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the nominal significant level for OS was 0.0001. The observed p-value was 0.0219.

Secondary analyses were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/comparisons in secondary hypothesis tests.

Findings:

Primary efficacy analysis is PFS analysis for the ITT population as assessed by the independent imaging core laboratory. Two hundred fifty PFS events were independently confirmed. An unstratified log-rank test was performed to compare PFS between the Sunitinib arm and the IFN-α arm in the ITT population.

The PFS analysis for the data collected until the cut-off date of November 15, 2005 included 96 events (25.6%) for PFS in the Sunitinib arm and 154 events (41.1%) for PFS in the IFN-α arm. Medians of PFS in the Sunitinib arm and the IFN-α arm were 47.3 weeks and 22.0 weeks respectively. The hazard ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm, was 0.415 (p-value < 0.000001).

The results from the unstratified log-rank test are presented in the Table 1 (same as reported by the sponsor).

Table 1. Primary Efficacy PFS Analysis in ITT Population

	Sunitinib	**IFN-α**
Number of patients (ITT)	375	375
Number of events (%)	96 (25.6%)	154 (41.1%)
Median[1] (weeks), 95% CI	47.3, (42.6,50.7)	22.0, (16.4, 24.0)
Unstratified Logrank test	P<0.000001	
Hazard ratio (95% CI)[2]	0.415(0.32, 0.54)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm.

2 Introduction

2.1 Overview

For the purpose of converting the accelerated approval to a regular approval, the sponsor submitted efficacy and safety data from Study A6181034, "A Phase 3, Randomized Study of Sunitinib versus Interferon-α (IFN-α) as First Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

2.1.1 Background

Growth of malignancies depends on cell-to-cell communication by directly triggering and maintaining the abnormal growth of malignant cells, and by indirectly driving the growth of supportive cells, such as the vasculature, upon which tumors depend.

Examples of the direct effect of cell-to-cell communication on oncogenesis include hormone-dependent prostate and breast tumors. In these tumors, malignant cells are oversensitive to circulating levels of hormones (testosterone and estrogen, respectively), and blockade of the production of hormone or of the hormone receptors are important therapeutic strategies in these diseases. Approximately 25 to 30% of breast cancers have amplification of the gene for the human epidermal growth factor-like receptor 2 (*HER2*) and/or over-express the gene product (HER2), and over-expression of HER2 has been associated with poor prognosis. In recent years, therapy has become more focused on signal transduction at the molecular level. Use of a targeted, humanized antibody against HER2 (trastuzumab or Herceptin®), in combination with chemotherapy, has resulted in significantly prolonged survival and increased objective responses, revolutionizing the treatment of HER2+ breast cancer. More recently, a molecularly targeted receptor tyrosine kinase (RTK) inhibitor (imatinib mesylate or STI571) has demonstrated efficacy in 2 tumor types; in gastrointestinal stromal tumors (GISTs) by its action on c-kit, an RTK constitutively activated by mutation in these tumors, and in chronic myeloid leukemia, through its inhibition of BCR-ABL, a constitutively active tyrosine kinase expressed in these patients. These findings suggest that agents targeted at specific second-messenger pathway abnormalities will continue to be developed as important therapeutic options in cancer patients.

Tumor growth also involves cell-to-cell communication indirectly by supporting the growth of neovasculature in growing tumors and metastases. In recent years, angiogenesis inhibitors have become important topics of research in oncology. Tumors without adequate vascularization become necrotic and/or apoptotic, and the number of microvessels in a primary tumor has been found to have prognostic

significance in several tumor types. Three growth factors that have been implicated in angiogenesis are vascular-endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). Each of these growth factors has more than 1 receptor; VEGF acts through 2 receptors, VEGFR Types 1 and 2; PDGF acts through 2 receptors, PDGFR-α and PDGFR-β ; and FGF has multiple forms that act on multiple FGF-receptors and their splice variants. Blockade of VEGFR2 has been shown to inhibit tumor growth *in vivo* and *in vitro*, and PDGF and FGF receptor expression have been identified in a variety of tumor types.

Sunitinib is a novel, small-molecule inhibitor of the PDGF and VEGF receptors, FLT-3, and c-kit. Sunitinib is expected to have therapeutic value both directly, by inhibition of RTKs on cancer cells, and indirectly, by inhibiting angiogenesis via PDGF and VEGF receptor inhibition. Consistent with its biochemical activity, Sunitinib inhibits the ligand-dependent tyrosine phosphorylation and the *in vitro* mitogenic response of human umbilical vein endothelial cells stimulated with VEGF, PDGF receptor-expressing NIH-3T3 cells stimulated with PDGF, and MO7E acute myeloid leukemia cells stimulated with stem cell factor. The sponsor reports that the oral administration of Sunitinib induces stasis or regression of large, established tumors in preclinical models, and its anti-tumor activity is associated with a reduction of tumor microvessel density. The sponsor reports Sunitinib also inhibits the growth of metastases in preclinical models.

With the exception of surgery and cytokine based treatment, there is currently a lack of therapies with a proven survival benefit. The response rate in patients treated with interleukin (IL)-2 and interferon-α (IFN-α) is low and responses are rarely durable. Combinations of IL-2 and IFN-α have been studied, but have not shown an overall survival advantage over monotherapy.

Of the 7 patients with metastatic RCC (MRCC) who were treated with Sunitinib on the Schedule 4/2 (4 weeks daily treatment followed by 2 weeks rest in repeated 6-week cycles) within the context of the Phase 1 program, 3 patients received 50 mg daily, 3 patients received 75 mg daily, and 1 patient received 100 mg every other day. All patients had received at least 1 prior anti-tumor therapy, and 5 had been treated with at least 1 prior cytokine-based therapy. The sponsor reports that the evidence of objective partial response (PR), without unacceptable toxicity, was observed in 4 patients with advanced RCC. In a Phase 2 study of 63 MRCC patients using Schedule 4/2, 23 patients (37%) had confirmed PRs. Per sponsor's reports, these observed responses in the Phase 1 and 2 setting with Schedule 4/2, along with the acceptable safety profile of Sunitinib at 50 mg daily, the high tumor vascularization, and the known expression of VEGFR and PDGFR in MRCC, provided clinical justification to further investigate the safety and efficacy of Sunitinib in patients with MRCC in a randomized clinical trial.

The sponsor submitted an application to evaluate the efficacy of single-agent Sunitinib in patients with progressive metastatic renal cell carcinoma who were refractory to 1 prior cytokine therapy (IFN, IL-2, or IFN + IL-2) on 10 August 2005. This application was for accelerated approval and the primary efficacy endpoint was the objective response rate (ORR). It was based primarily on data from the Phase II study, A6181006. Supportive data were provided from the Phase II study (RTKC-0511-014) in the same patient population. The FDA granted accelerated approval for Sunitinib on 26 January 2006 for advanced renal cell carcinoma (RCC). On 20 December 2005, the FDA also granted a regular approval for Sorafenib for the treatment of patients with advanced renal cell carcinoma.

In the current submission, for the purpose of converting the accelerated approval to a regular approval, the sponsor submitted efficacy and safety data from Study A6181034, "A Phase 3, Randomized Study of Sunitinib versus Interferon-α as First Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

2.1.2 Statistical Issues

According to the protocol, PFS data were censored on the day following the date of the last on-treatment (including 28 day follow-up period) tumor assessment documenting absence of PD for subjects who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment or were removed from treatment prior to documentation of objective tumor progression. It was shown in the PFS analysis that the lack of radiographic monitoring of patients after the 28 day follow-up caused a convergence of two PFS curves at about 48 to 50 weeks.

The lack of radiographic monitoring of patients after the 28 day follow-up was also the reason for the convergence of two time-to-progression (TTP) curves at about 48 to 50 weeks.

The second interim analysis was for PFS analysis which was planed when approximately 354 events have occurred (approximately 75% of the total number of events expected). As of the data cutoff date (15 November 2005) for the interim PFS analysis, 750 subjects had been randomized in Study A6181034; these 750 subjects comprised the ITT population. Three hundred seventy-five subjects were randomized to the Sunitinib arm, and 375 were randomized to the IFN-α arm. Two hundred fifty PFS events were independently confirmed. Assuming a 2-sided test with the observed number of events (250), accounting for the one prior ORR interim analysis that occurred after 83 PFS events had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the lower

limit of the log-rank statistic that would indicate stopping for efficacy would be 2.875 and the nominal significant level was 0.0042. The observed log-rank statistic was 6.8524 and the observed p-value was less than 0.000001.

Because the data were not yet mature, median OS had not been achieved on either treatment arm. The hazard ratio for OS was 0.650 (95% CI: 0.449 to 0.942; p = 0.0219); which was not statistically significant based on the stopping boundaries for this interim analysis. Accounting for the one prior ORR interim analysis that occurred after 29 deaths had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the nominal significant level for OS was 0.0001. The observed p-value was 0.0219.

Secondary analyses were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/comparisons in secondary hypothesis tests.

2.2 Data Sources

Data used for review is from the following electronic submissions: the submission No. 003 received on March 31, 2006 (the network path \\CDSESUB1\EVSPROD\NDA021968\0025) and the submission N0. 005 received on August 9, 2006 (the network path \\CDSESUB1\EVSPROD\NDA021968\021968.ENX).

3 Statistical Evaluation

3.1 Evaluation of Efficacy

As of the data cutoff date (15 November 2005) for the interim PFS analysis, 750 subjects had been randomized in Study A6181034; these 750 subjects comprised the ITT population. Three hundred seventy-five subjects were randomized to the Sunitinib arm, and 375 were randomized to the IFN-α arm.

3.1.1 Study Design

Study A6181034 was a randomized, multi-center, international, phase 3 study of Sunitinib vs. IFN-α as first-line therapy in subjects with MRCC. Subjects received treatment with either Sunitinib in repeated 6-week cycles, consisting of 4 weeks of 50 mg daily Sunitinib administration followed by 2 weeks off treatment (Schedule 4/2), or IFN-cc, administered as a subcutaneous injection on 3 non-consecutive days each week. An open-label study was necessitated by the differing routes and administration for the 2 treatment arms.

The primary endpoint of this study is PFS. Disease progression and other endpoints based on objective tumor measurements were reviewed by an independent, third-party imaging laboratory that was blinded to the treatment assignment.

Reviewer's Comments:

The sponsor designed Study A6181034 for the purpose of converting the accelerated approval to a regular approval.

3.1.2 Study Objectives

The primary objective of Study A6181034 was to compare the PFS associated with Sunitinib versus that associated with Interferon-α (IFN-α) for the first-line treatment of subjects with metastatic renal cell carcinoma.

Secondary objectives included the following:

- To compare the objective response rate (ORR) associated with sunitinib malate versus that associated with IFN-a for the first-line treatment of MRCC
- To compare the overall survival (OS) associated with sunitinib malate versus that associated with IFN-α for the first-line treatment of subjects with metastatic renai cell carcinoma
- To compare the time to tumor progression (TTP) associated with sunitinib malate versus that associated with IFN-α for the first-line treatment of subjects with metastatic renal cell carcinoma

3.1.3 Efficacy Endpoints

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, which ever occurs first. Tumor response and progression was confirmed by an independent imaging core laboratory.

If tumor progression data included more than 1 date, the first date was used. PFS was calculated as (first event date- the date of randomization +1)/7. PFS data was censored on the day following the date of the last on treatment (including 28 day follow-up period) tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression. Patients lacking an evaluation of

tumor response after randomization had their event time censored on the date of randomization with a duration of 1 day.

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 1 date, the first date was used. TTP was calculated as (first event date- the date of randomization +1)/7. TTP data were censored on the day following the date of the last on treatment (including 28 day follow-up period) tumor assessment documenting absence of progressive disease for patients who did not have objective tumor progression while on treatment or who were given anti-tumor treatment other than the study treatment prior to observing objective tumor progression. Patients lacking an evaluation of tumor response after randomization had their event time censored on the date of randomization with a duration of 1 day.

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 all randomized patients. Confirmed responses are those that persist on repeat imaging study ≥4 weeks after initial documentation of response. Third-party review and qualification were performed retrospectively by the core laboratory. Patients who did not have on-study radiographic tumor re-evaluation or who died, progressed or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR.

Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. OS was calculated as (the event date – the date of randomization +1)/7. For patients who were alive, their survival times were censored at the last date they are known to be alive. Patients lacking data beyond the day of randomization had their survival times censored at the date of randomization with a duration of 1 day. Death was determined from AE data (where the outcome is death) or from follow-up contact data (where the patient current status is death, or the patient is alive). Patients crossing over to the Sunitinib treatment arm after discontinuing treatment with IFN-α were included in the OS analyses as per their original randomization.

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 any cause, whichever occurs first. If tumor progression data included more than 1 date, the first date was used. Duration of tumor response was calculated as (the end date for DR – first CR or PR that is subsequently confirmed +1)/7. DR data were censored on the day following the date of the last on treatment (including 28 day follow-up period) tumor assessment documenting absence of progressive disease for patients who did not

have objective tumor progression and who did not die due to any cause while on treatment or who were given antitumor treatment other than the study treatment prior to observing objective tumor progression. DR was calculated for the subgroup of patients with objective response.

DR was planned to be determined from oncologic assessment data (where data meet the criteria for PD or where the investigator assesses the patient as having PD), from the EOS evaluation (where reason for discontinuation is 'Lack of efficacy'), or from AE data (where the outcome is death).

Reviewer's Comments:

According to the protocol, PFS data were censored on the day following the date of the last on-treatment (including 28 day follow-up period) tumor assessment documenting absence of PD for subjects who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment or were removed from treatment prior to documentation of objective tumor progression. It was shown in the PFS analysis that the lack of radiographic monitoring of patients after the 28 day follow-up caused a convergence of two PFS curves at about 48 to 50 weeks.

3.1.4 Sample Size Considerations

A total of 471 PFS events were required for a 2-sided, unstratified log-rank test with an overall 2-sided significance level of 0.05 and power of 0.90 to detect a 35% improvement in median PFS from 20 weeks to 27 weeks in patients eandomized to receive Sunitinib. Applying a 1:1 randomization and a planned accrual period of 12 months, a minimum follow-up period of 4 months, and an expectation that approximately 5% of patients might be lost to follow-up within 6 months, it was estimated that 690 patients needed to be enrolled in order to observe 471 events by the end of the minimum follow-up period. The nominal significance level for the interim and final efficacy analyses were determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule. The final analysis was planned when the 471st events are observed.

The sample size described above also allowed the assessment of differences in the secondary endpoint of OS with a high level of significance. A total of 390 events were required for a 2-sided, unstratified log-rank test with an overall 2-sided significance level of 0.05 and power of 0.85. This assumed a 35.7% improvement (hazard ratio 0.74 [the Sunitinib vs. the IFN-α arm]) in median OS from 56 weeks to 76 weeks in patients randomized to receive Sunitinib, a minimum follow-up period of approximately 12 months. The estimated sample size of 690 patients for PFS would also be sufficient to observe the 390 events needed for comparing median OS.

Two interim analyses were planed. The planned first interim analysis was for ORR analysis after the first 250 patients would have completed at least 3 cycles of treatment (slightly more than one-third of the total number of patients expected to enroll in the study). The planned second interim analysis was for PFS analysis when approximately 354 events would have occurred (approximately 75% of the total number of events expected).

Reviewer's Comments:

At the time of data cutoff for the interim ORR analysis (4 July 2005), 253 subjects were randomized: 129 in the Sunitinib arm and 124 in the IFN-α arm.

As of the data cutoff date (15 November 2005) for the interim PFS analysis, 750 subjects (compared to planned 690 patients) had been randomized in Study A6181034; these 750 subjects comprised the ITT population. Three hundred seventy-five subjects were randomized to the Sunitinib arm, and 375 were randomized to the IFN-α arm. Two hundred fifty PFS events (compared to planned 354 events) were independently confirmed.

3.1.5 Efficacy Analysis Methods

The primary efficacy analysis was based on the ITT population which includes all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. This study would be considered a positive trial if the unstratified log-rank test for PFS is significant at a 2-sided significance level of 0.05 in favor of Sunitinib. Estimates of time-to-event endpoints were obtained using Kaplan-Meier methods.

Complete response rates (CR), partial response rates (PR), and the ORR were assessed by calculating 2-sided 95% confidence intervals based on the binomial distribution.

Reviewer's Comments:

Secondary analyses were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/comparisons in secondary hypothesis tests.

3.1.6 Sponsor's Results and Statistical Reviewer's Findings/ Comments

As of the data cutoff date (15 November 2005) for the interim PFS analysis, 750 subjects had been randomized in Study A6181034; these 750 subjects comprised the ITT population. Three hundred seventy-five subjects (50%) were randomized

to the Sunitinib arm, and 375 (50%) were randomized to the IFN-a arm. The ITT population is the primary population for evaluating all efficacy endpoints as well as subject characteristics.

3.1.6.1 Baseline Characteristics

The baseline Characteristics of the overall population are presented in Table 2.

Table 3. Baseline Characteristics of the Patients in the Study A6181034

Characteristic	Sunitinib (N=375)	INF-α (N=375)
Age — yr		
Mean (SD)	60.6 (10.1)	60.1 (9.5)
Median (Range)	62.0 (27–87)	59.0 (34–85)
Age grouped — no. (%)		
<65	223 (59.5)	252 (67.2)
+65	152 (40.5)	123 (32.8)
Sex — no. (%)		
Male	267 (71.2)	269 (71.7)
Female	108 (28.8)	106 (28.3)
Race — no. (%)		
Caucasian	354 (94.4)	340 (90.7)
Black	4 (1.1)	9 (2.4)
Oriental/Asian	7 (1.9)	12 (3.2)
Others	10 (2.7)	14 (3.7)
ECOG performance-status — no. (%)		
0	231 (61.6)	229 (61.1)
1	144 (38.4)	142 (37.9)
2	0 (0.0)	4 (1.1)
LDH — no. (%)		
>1.5xULN	15 (4.0)	20 (5.3)
≤1.5xULN	360 (96.0)	338 (90.1)
Missing	0 (0.0)	17 (4.5)
Hemoglobin — no. (%)		
<LLN	98 (26.1)	121 (32.3)
≥LLN	277 (73.9)	238 (63.5)
Missing	0 (0.0)	16 (4.3)
Corrected Calcium — no. (%)		
>10 mg/dL	29 (7.7)	17 (4.5)
≤10 mg/dL	346 (92.3)	342 (91.2)
Missing	0 (0.0)	16 (4.3)
Time since initial diagnosis — wks		
Median (Range)	45.7 (0.6–1278.7)	44.4 (1.3–1115.1)
Metastatic sites — no. (%)		
Lung	292 (77.9)	298 (79.5)
Lymph Nodes	218 (58.1)	198 (52.8)
Bone	112 (29.9)	112 (29.9)
Liver	99 (26.4)	90 (24.0)
Visceral Organs	63 (16.8)	63 (16.8)
Local Recurrence	63 (16.8)	56 (14.9)
Soft Tissue	59 (15.7)	56 (14.9)

Reviewer's Comments:

In the overall patient population the baseline characteristics appear to be balanced between the two treatment arms. However, there were more missing values in the control arm with respect to LDH, hemoglobin and corrected calcium.

3.1.6.2 Primary Efficacy Analyses

Progression-free Survival Analysis

Primary efficacy analysis is PFS analysis for the ITT population as assessed by the independent imaging core laboratory. Two hundred fifty PFS events were independently confirmed. An unstratified log-rank test was performed to compare PFS between the Sunitinib arm and the IFN-α arm in the ITT population.

The PFS analysis for the data collected until the cut-off date of November 15, 2005 included 96 events (25.6%) for PFS in the Sunitinib arm and 154 events (41.1%) for PFS in the IFN-α arm. Medians of PFS in the Sunitinib arm and the IFN-α arm were 47.3 weeks and 22.0 weeks respectively. The hazard ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm, was 0.415 (p-value < 0.000001).

The results from the unstratified log-rank test are presented in the Table 4 (same as reported by the sponsor). The Kaplan-Meier curves for the ITT population are illustrated in Figure 1.

Table 4. Primary Efficacy PFS Analysis in ITT Population

	Sunitinib	IFN-α
Number of patients (ITT)	375	375
Number of events (%)	96 (25.6%)	154 (41.1%)
Median[1] (weeks), 95% CI	47.3, (42.6,50.7)	22.0, (16.4, 24.0)
Unstratified Logrank test	P<0.000001	
Hazard ratio (95% CI)[2]	0.415(0.32, 0.54)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm.

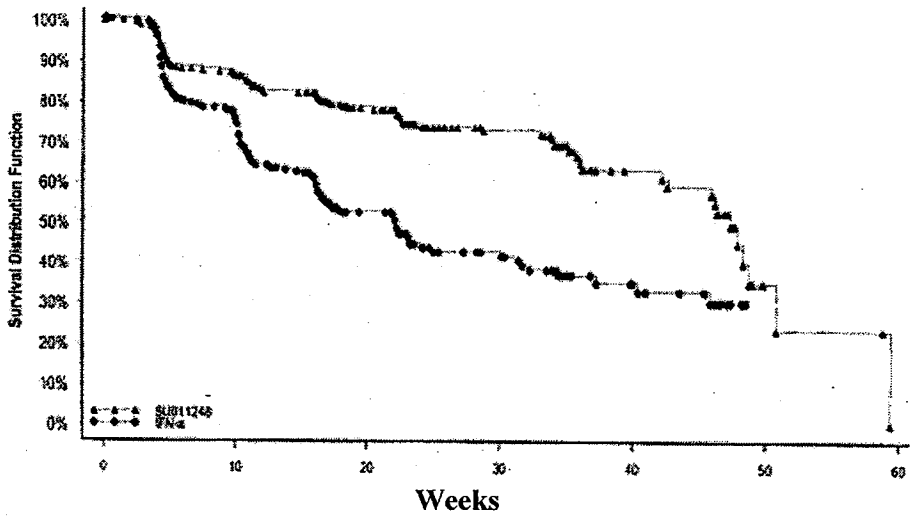

Figure 1: Kaplan-Meier Curves for PFS in the ITT Population (Source: Figure 14.1.1.1.1 in the sponsor's CSR)

Reviewer's Comments:

Assuming a 2-sided test with the observed number of events (250), accounting for the one prior ORR interim analysis that occurred after 83 PFS events had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the lower limit of the log-rank statistic that would indicate stopping for efficacy was 2.875 and the nominal significant level was 0.0042. The observed log-rank statistic was 6.8524 and the observed p-value was less than 0.000001.

According to the protocol, PFS data were censored on the day following the date of the last on-treatment (including 28 day follow-up period) tumor assessment documenting absence of PD for subjects who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment or were removed from treatment prior to documentation of objective tumor progression. As shown in Figure 1, the 2 lines converge at about 48 to 50 weeks. This convergence reflects the lack of radiographic monitoring of patients after the 28 day follow-up. Another reason for this convergence was that few subjects on either treatment arm had the opportunity to remain on study for more than 50 weeks at the time of analysis.

3.1.6.3 Secondary Efficacy Analyses

The protocol specified secondary endpoints included overall response rate (ORR), time to progression (TTP), and overall survival (OS). Because the data for OS are not yet mature, this section will focus on ORR and TTP analyses. As per the protocol, the ORR and TTP analyses were conducted in the ITT population.

Overall Response Rate

At the time of data cutoff for the interim ORR analysis (4 July 2005), 253 subjects were randomized: 129 in the Sunitinib arm and 124 in the IFN-α arm. The interim analysis for the ORR based on the core imaging laboratory results identified 33 (25.6%) versus 9 (7.3%) partial responses on Sunitinib vs. the IFN-α arm, respectively (Table 5).

At the time of data cutoff for the interim PFS analysis (15 November 2005), 750 subjects were randomized: 375 in the Sunitinib arm and 375 in the IFN-α arm. The analysis for the ORR based on the core imaging laboratory results identified 103 (27.5%) versus 20 (5.3%) partial responses on Sunitinib versus IFN-α, respectively (Table 5); of these subjects, 16 (15.5% subjects with responses) vs. 0 (0.0% subjects with responses) subsequently progressed or died. Median duration of response (DR) was 40.9 weeks (95% CI: 30. 1 to 54.1 weeks) on Sunitinib. Duration of response on IFN- α could not be calculated because no subjects had subsequent progression or death.

Table 5. Overall Confirmed Tumor Response by Core Imaging Lab.

Response	Sunitinib	IFN-α
Data cut-off date: 4 July 2005	N=129	N=124
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	33 (25.6)	9 (7.3)
Stable disease	53 (41.1)	54 (43.5)
Progressive disease (PD)	25 (19.4)	29 (23.4)
Not evaluated	4 (3.1)	14 (11.3)
Missing for core lab assessment	14 (10.9)	18 (14.5)
ORR (CR+PR) % (95% CI)	25.6% (18.3%-34.0%)	7.3% (3.4%-13.3%)
Data cut-off date: 15 November 2005	N=375	N=375
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	103 (27.5)	20 (5.3)
Stable disease	160 (42.7)	160 (42.7)
Progressive disease (PD)	52 (13.9)	99 (26.4)
Not evaluated/ Missing	60 (16.0)	96 (25.3)
ORR (CR+PR) % (95% CI)	27.5% (23.0%-32.3%)	5.3% (3.3%-8.1%)
P-value for ORR comparison	<0.001	

The sponsor also submitted updated response rate analysis for Study A6181006 that evaluated Sunitinib in patients with cytokine-refractory MRCC. Based on updated efficacy assessments through December 2005, the core imaging laboratory reported 38 partial responses, yielding an ORR of 35.8% (95% CI = 26.8–45.7) (Sn 004). Median duration of response has not yet been reached.

Reviewer's Comments:

Duration of response at the time of the first interim analysis for ORR was not presented because data for duration of response were not yet mature at the time.

Time to Tumor Progression

TTP is summarized for the ITT population, based upon the central radiologist assessments, in Table 6 and in Figure 2. At the time of the interim PFS analysis, 90 (24.0%) vs. 142 subjects (37.9%) on the Sunitinib arm vs. the IFN-α arm, respectively, had experienced objective tumor progression. The median TTP was 47.9 (95% CI: 45.9 to 50.7 weeks) vs. 22.3 weeks (95% CI: 17.3 to 31.3 weeks) with a hazard ratio of 0.416 (95% CI: 0.318 to 0.545; p <0.000001).

Table 6. Primary Efficacy TTP Analysis in ITT Population

	Sunitinib	**IFN-α**
Number of patients (ITT)	375	375
Number of events (%)	90 (24.0%)	142 (37.9%)
Median[1] (weeks), 95% CI	47.9, (45.9, 50.7)	22.3, (17.3, 31.3)
Unstratified Logrank test	P<0.000001	
Hazard ratio (95% CI)[2]	0.416 (0.32, 0.54)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm.

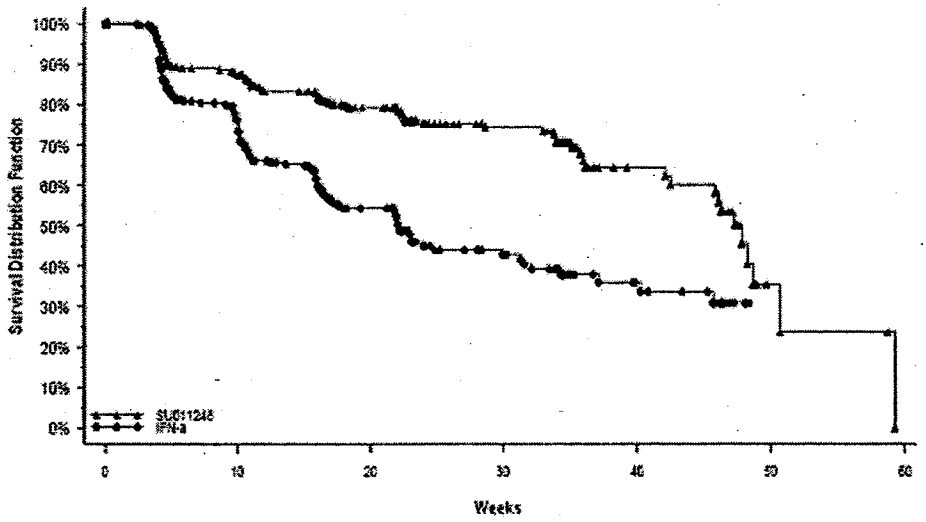

Figure 2: Kaplan-Meier Curves for TTP in the ITT Population
(Source: Figure 14.1.2.1.1 in the sponsor's CSR)

Reviewer's Comments:

As shown in Figure 2, the 2 lines converge at about 48 to 50 weeks. Again, this convergence reflects the lack of radiographic monitoring of patients after the 28 day follow-up and few subjects on either treatment arm who had the opportunity to remain on study for more than 50 weeks at the time of analysis.

Overall Survival Analysis

Forty-nine (13. 1%) vs. 65 subjects (17.3%) on Sunitinib vs. IFN-α, respectively, were known to have died at the time of the interim PFS analysis. Data for subjects not known to have died were censored at the time they were last known to be alive. OS is summarized for the ITT population in Table 7, and a Kaplan-Meier curve of OS is presented in Figure 3. The hazard ratio was 0.650 (95% CI: 0.449 to 0.942; p = 0.0219); which was not statistically significant based on the stopping boundaries for this interim analysis.

Table 7. Overall Survival Analysis in ITT Population

	Sunitinib	IFN-α
Number of patients (ITT)	375	375
Number of events (%)	49 (13.1%)	65 (17.3%)
Median[1] (weeks), 95% CI	-	-
Unstratified Logrank test	P=0.0219	
Hazard ratio (95% CI)[2]	0.650 (0.449, 0.942)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm.

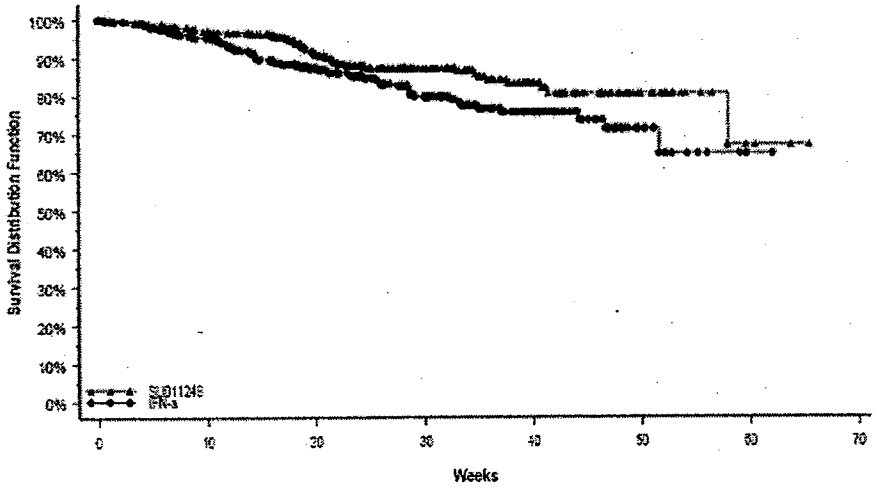

Figure 3: Kaplan-Meier Curves for OS in the ITT Population
(Source: Figure 14.1.3.1.1 in the sponsor's CSR)

Reviewer's Comments:

Because the data were not yet mature, median OS had not been achieved on either treatment arm. The hazard ratio for OS was 0.650 (95% CI: 0.449 to 0.942; p = 0.0219); which was not statistically significant based on the stopping boundaries for this interim analysis. Accounting for the one prior ORR interim analysis that occurred after 29 deaths had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the nominal significant level for OS was 0.0001. The observed p-value was 0.0219.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

This section will focus on PFS analyses by gender (male vs. female, Table 8), age (< 65 years vs. ≥ 65 years, Table 9) and race (white vs. non-white, Table 10). For each subgroup population, a separate unadjusted log-rank test was performed.

Table 8. PFS Analyses by Gender in ITT Population

	Sunitinib	IFN-α
Gender		
Male		
Number of patients (ITT)	267	269
Number of events (%)	72 (27.0%)	103 (38.3%)
Median (weeks), 95% CI[1]	47.9 (42.1, 48.7)	22.3 (17.1, 40.3)
Hazard ratio [95% CI][2]	0.47 (0.35, 0.64)	
Unadjusted log-rank test	P-value[3]<0.00001	
Female		
Number of patients (ITT)	108	106
Number of events (%)	24 (22.2%)	51 (48.1%)
Median (weeks), 95% CI[1]	46.3 (46.1, 50.7)	16.0 (10.3, 22.1)
Hazard ratio (95% CI)[2]	0.30 (0.18, 0.49)	
Unadjusted log-rank test	P-value[3]<0.00001	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm; [3]: not adjusted for multiple analyses.

Table 9. PFS Analyses by Age in ITT Population

	Sunitinib	IFN-α
Age		
<65		
Number of patients (ITT)	223	252
Number of events (%)	63 (28.3%)	108 (42.9%)
Median (weeks), 95% CI[1]	46.3 (42.1, 48.3)	17.3 (16.0, 23.0)
Hazard ratio (95% CI)[2]	0.41 (0.30, 0.56)	
Uadjusted log-rank test	P-value[3]<0.00001	
>=65		
Number of patients (ITT)	152	123
Number of events (%)	33 (21.7%)	46 (37.4%)
Median (weeks), 95% CI[1]	48.7 (35.7, -)	23.1 (16.4, 34.3)
Hazard ratio (95% CI)[2]	0.43 (0.28, 0.69)	
Uadjusted log-rank test	P-value[3]=0.0002	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the sorafenib arm, as compared with the placebo arm; [3]: not adjusted for multiple analyses.

Table 10. PFS Analyses by Race in ITT Population

	Sunitinib	IFN-α
Race		
White		
Number of patients (ITT)	354	340
Number of events (%)	87 (24.6%)	138 (40.6%)
Median (weeks), 95% CI[1]	46.3 (42.1, -)	22.1 (16.4, 24.9)
Hazard ratio [95% CI][2]	0.42 (0.32, 0.56)	
Unadjusted log-rank test	P-value[3]<0.00001	
Non-white		
Number of patients (ITT)	21	35
Number of events (%)	9 (42.9%)	16 (45.7%)
Median (weeks), 95% CI[1]	48.3 (42.6, 59.3)	17.7 (9.9, -)
Hazard ratio (95% CI)[2]	0.35 (0.13, 0.98)	
Unadjusted log-rank test	P-value[3]=0.0362	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm; [3]: not adjusted for multiple analyses.

Reviewer's Comments:

The treatment effect appears to be similar across all subgroups.

5 Summary and Conclusions

For the purpose of converting the accelerated approval to a regular approval, the sponsor submitted efficacy and safety data from a confirmatory Study A6181034, "A Phase 3, Randomized Study of Sunitinib versus Interferon-α (IFN-α) as First Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

5.1 Statistical Issues and Collective Evidence

Primary efficacy analysis of Study A6181034 is PFS analysis for the ITT population as assessed by the independent imaging core laboratory. At the time of data cutoff for the interim PFS analysis (15 November 2005), 750 subjects were randomized: 375 in the Sunitinib arm and 375 in the IFN-α arm. The PFS analysis included 96 events (25.6%) for PFS in the Sunitinib arm and 154 events (41.1%) for PFS in the IFN-α arm.

Statistical Issues:

According to the protocol, PFS data were censored on the day following the date of the last on-treatment (including 28 day follow-up period) tumor assessment documenting absence of PD for subjects who did not have objective tumor progression and who did not die due to any cause while on treatment or who were given anti-tumor treatment other than the study treatment or were removed from

treatment prior to documentation of objective tumor progression. It was shown in the PFS analysis that the lack of radiographic monitoring of patients after the 28 day follow-up caused a convergence of two PFS curves at about 48 to 50 weeks.

The lack of radiographic monitoring of patients after the 28 day follow-up was also the reason for the convergence of two TTP curves at about 48 to 50 weeks.

The second interim analysis was for PFS analysis which was planed when approximately 354 events have occurred (approximately 75% of the total number of events expected). As of the data cutoff date (15 November 2005) for the interim PFS analysis, 750 subjects had been randomized in Study A6181034; these 750 subjects comprised the ITT population. Three hundred seventy-five subjects were randomized to the Sunitinib arm, and 375 were randomized to the IFN-α arm. Two hundred fifty PFS events were independently confirmed. Assuming a 2-sided test with the observed number of events (250), accounting for the one prior ORR interim analysis that occurred after 83 PFS events had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the lower limit of the log-rank statistic that would indicate stopping for efficacy would be 2.875 and the nominal significant level was 0.0042. The observed log-rank statistic was 6.8524 and the observed p-value was less than 0.000001.

Because the data were not yet mature, median OS had not been achieved on either treatment arm. The hazard ratio for OS was 0.650 (95% CI: 0.449 to 0.942; p = 0.0219); which was not statistically significant based on the stopping boundaries for this interim analysis. Accounting for the one prior ORR interim analysis that occurred after 29 deaths had been observed, and using the Lan-DeMets spending function approach with an O'Brien-Fleming 2-sided boundary for efficacy only, computing the boundary for the observed number of events at the time of the interim PFS analysis, the nominal significant level for OS was 0.0001. The observed p-value was 0.0219.

Secondary analyses were tested at a significance level of 0.05. No adjustments and no prioritization were planned for multiple testings/comparisons in secondary hypothesis tests.

5.2 Conclusions and Recommendations

Primary efficacy analysis of Study A6181034 is PFS analysis for the ITT population as assessed by the independent imaging core laboratory. At the time of data cutoff for the interim PFS analysis (15 November 2005), 750 subjects were randomized: 375 in the Sunitinib arm and 375 in the IFN-α arm. The PFS analysis included 96 events (25.6%) for PFS in the Sunitinib arm and 154 events (41.1%)

for PFS in the IFN-α arm. Estimated medians of PFS in the Sunitinib arm and the IFN-α arm were 47.3 weeks and 22.0 weeks respectively. The hazard ratio for recurrence or death in the Sunitinib arm, as compared with the IFN-α arm, was 0.415 (p-value < 0.000001).

At the time of PFS analysis, the analysis for the ORR based on the core imaging laboratory results identified 103 (27.5%) versus 20 (5.3%) partial responses on Sunitinib versus IFN-α, respectively; of these subjects, 16 (15.5% subjects with responses) vs. 0 (0.0% subjects with responses) subsequently progressed or died. Median duration of response (DR) was 40.9 weeks (95% CI: 30. 1 to 54.1 weeks) on Sunitinib. Duration of response on IFN-α could not be calculated because no subjects had subsequent progression or death.

The submitted data support the claim based on PFS analysis. Whether the endpoint and the size of the effect on the primary endpoint in Study A6181034 are adequate for converting the accelerated approval to a regular approval is deferred to clinical judgment.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Shenghui Tang, Ph.D.

Date:

Concurring Reviewer: Rajeshwari Sridhara, Ph.D., Team Leader
Aloka Chakravarty, Ph.D., Director

Date:

cc:
HFD-150/V. Goodman
HFD-150/A. Ibrahim
HFD-711/R. Sridhara
HFD-711/S. Tang
HFD-711/A. Chakravarty
HFD-700/R. O'Neill
HFD-700/L. Patrician

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/s/

Shenghui Tang
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Aloka Chakravarty
1/18/2007 03:56:35 PM
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-938 (GIST): SLR 002, SE8 003, SE8 004, SE8 005

Drug name:	SUTENT™
Generic name:	Sunitinib malate
Formulation:	Capsules for oral administration (12.5 mg, 25 mg, 50 mg equivalent)
Indication:	1) Treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. 2) Treatment of advanced renal cell carcinoma.
Applicant:	Pfizer Inc. 10777 Science Center Dr San Diego, CA 92121
OCPB Division:	Division of Clinical Pharmacology and Biopharmaceutics 5
OND Division:	Division of Drug Oncology Products (HFD-150)
Submission Dates:	30-Mar-2006, 1-Aug-2006, 9-Aug-2006, 29-Sep-2006, 2-Oct-2006, 17-Nov-2006, 12-Dec-2006
OCP Reviewer:	Roshni Ramchandani, Ph.D.
Pharmacometrics Reviewer:	Roshni Ramchandani, Ph.D.
OCP Secondary Reviewer:	Brian Booth, Ph.D.
Pharmacometrics Secondary Reviewer:	Joga Gobburu, Ph.D.
Type of Submission:	NDA-Supplemental

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Sunitinib (SU011248) is a small molecule, multi-targeted receptor tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinases (RTKs). Sunitinib has been previously approved for 1) treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate, and 2) treatment of advanced renal cell carcinoma.

The current submission is a supplemental NDA for sunitinib. It includes two clinical study reports and a data analysis report submitted in fulfillment of the following phase 4 commitments: 1) evaluation of the effect of sunitinib on QTc interval, 2) evaluation of pharmacokinetics of sunitinib subjects with impaired hepatic function, 3) exposure-response analyses of sunitinib in treatment-naïve and cytokine refractory renal cell carcinoma patients in phase 2 and 3 clinical studies.

The results of the QTc study indicated that at therapeutic concentrations, sunitinib prolongs the QT interval. The results of the hepatic impairment study indicated that mean Cmax and AUC for sunitinib and its primary active metabolite, SU012662, were similar between subjects with mild and moderate hepatic impairment and normal subjects. Exposure-efficacy analyses were performed to evaluate the relationship between sunitinib exposure (AUC) and three measures of efficacy, time to tumor progression, response rates and changes in tumor size. Data was pooled across the studies in cytokine-refractory and treatment-naïve patients. There was no significant relationship between AUC and time to tumor progression or death, possibly due to the small number of patients with observed data among the treatment-naïve patients. Analysis of response rates showed a significant correlation of AUC of sunitinib with the probability of a partial response in cytokine-refractory patients.

1.1. Recommendations

The Office of Clinical Pharmacology finds the studies submitted by the applicant to be **acceptable, and in fulfillment of the applicant's post-marketing commitments as described** below.

Post marketing commitments:

1. **Submit the completed report and datasets for study titled "A phase 1 study to evaluate the** effect of SU011248 on QTc interval in subjects **with advanced solid tumors" (PMC #7).**

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" (PMC #8).**

3. 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" (PMC #6).**

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

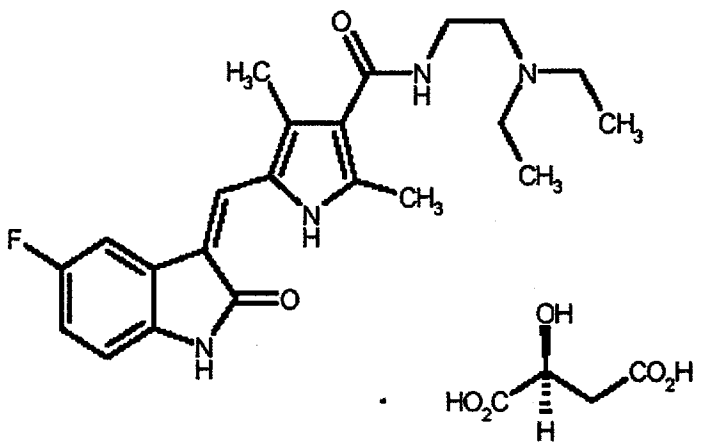
2. QUESTION BASED REVIEW

2.1. GENERAL ATTRIBUTES OF THE DRUG

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Sunitinib (SU011248) is a small molecule, multi-targeted receptor tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinases (RTKs). Sunitinib is known 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. Sunitinib malate is the malate salt of SU011248 (the free base). The chemical structures of sunitinib and its L-malate salt are represented in Fig. 1.

Figure 1: Chemical Structures of Sunitinib and L-Malate Counter Ion.



Sunitinib **L-malate counter ion**

Molecular weight:	398 Daltons (sunitinib),	523 Daltons (sunitinib malate)
Molecular formula:	$C_{22}H_{27}FN_4O_2$ (sunitinib),	$C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$ (sunitinib malate)

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Sunitinib (SU011248) is an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Inhibition of the tyrosine kinase activity of these RTKs by sunitinib was demonstrated in biochemical and

cellular assays, and inhibition of function was demonstrated in cell proliferation assays. The primary metabolite of sunitinib, SU012662, exhibits similar potency compared to sunitinib in biochemical and cellular assays.

The target plasma concentration (sunitinib + SU012662) for inhibition of RTK targets is ≥ 50 ng/mL (approximately 0.005 μM free plasma concentration). The median C_{max} plasma concentrations (sunitinib + SU012662) observed at relevant doses in clinical studies ranged from 100-125 ng/mL (approximately 0.01 μM free plasma concentration).

Sunitinib has been approved for 1) treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate, and 2) treatment of advanced renal cell carcinoma.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dose of SUTENT is 50 mg given orally once daily for 4 weeks followed by 2 weeks off. SUTENT can be taken with or without food.

2.2 CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The current submission includes two clinical study reports and a data analysis report submitted in fulfillment of Phase 4 commitments made by the sponsor at the time of the original approval of the NDA for sunitinib.

1) The effect of sunitinib on QTc interval in patients with advanced solid tumors (post-marketing commitment item 7).
2) A phase 1 study to evaluate the pharmacokinetics of sunitinib subjects with impaired hepatic function (post-marketing commitment item 8).
3) Exposure-response of sunitinib in treatment-naïve and cytokine refractory renal cell carcinoma patients in phase II and III clinical studies (post-marketing commitment item 6).

<u>Effect of sunitinib on QTc interval (study A6181005):</u>
This study was a single-blind study in patients with advanced solid tumors. Patients underwent serial electrocardiogram (ECG) assessments on Day -1 (baseline), then received a single dose of moxifloxacin on Day 1 and a single dose of placebo on Day 2, followed by a 1-week course of SU011248 (loading dose (LD) on Days 3 and 9, maintenance dose on Days 4-8). In order to minimize the probability of inducing nausea and or vomiting, all subjects were pretreated with intravenous granisetron (1 mg) prior to dosing on Days 3 and 9. Granisetron was also administered to subjects on Day 2 (placebo only day) in order to assess its effect on ECG.

<u>Effect of hepatic impairment on sunitinib PK (study A6181079):</u>
This was an open-label, single-dose, parallel-group study to evaluate the effects of mild and

moderate impaired hepatic function on the single-dose pharmacokinetics of sunitinib and its active metabolite, SU012662 in subjects with mild and moderate impaired hepatic function. The study was conducted in three groups (8 subjects per group) with the following degrees of hepatic function: Group 1: subjects with normal hepatic function, Group 2: subjects with mild hepatic impairment (Child-Pugh classification A, score 5-6), and Group 3: subjects with moderate hepatic impairment (Child-Pugh classification B, score 7-9). All subjects in all groups received a single 50-mg dose of sunitinib. Serial blood samples were collected for analysis of sunitinib and SU012662 levels. PK parameters were estimated for sunitinib and SU012662 for each individual and compared across the three groups.

Exposure-response relationships for sunitinib in renal cell cancer patients:
The primary objective was to compare the progression-free survival (PFS) associated with sunitinib malate versus that associated with interferon-alfa (IFN-a) for the first-line treatment of subjects with metastatic renal cell carcinoma (MRCC). Secondary objectives were to compare the objective response rate (ORR), overall survival (OS), time to tumor progression (TTP) and patient-related outcomes between sunitinib and IFN-a in these patients. In addition, the sponsor had planned to evaluate sunitinib and SU012662 trough plasma concentrations (Ctrough) and to correlate these plasma concentrations with efficacy and safety parameters in a subset of subjects; and to assess and explore correlations of potential biomarkers with cancer and treatment-related outcomes in a subset of subjects. Subjects received either sunitinib malate or IFN-a. Sunitinib malate was administered as an oral capsule at a starting dose of 50 mg daily for 4 weeks followed by 2 weeks off treatment in repeated 6-week cycles of treatment. IFN-a (Roferon-A, Roche) was administered as a subcutaneous injection in 6-week cycles on 3 non-consecutive days per week; Subjects received 3 MU per dose during the first week, 6 MU per dose the second week, and 9 MU per dose thereafter.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Pharmacodynamic endpoints evaluated in the phase 3 study included progression-free survival (PFS), overall survival, overall response rates, as well as changes in tumor volume.
PFS was the primary endpoint in this study and was defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause.
ORR was defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST, relative to the total population of randomized subjects. Confirmed responses were those that persisted on repeat imaging study 2 4 weeks after initial documentation of response.
Overall survival was defined as the time from date of randomization to date of death due to any cause.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

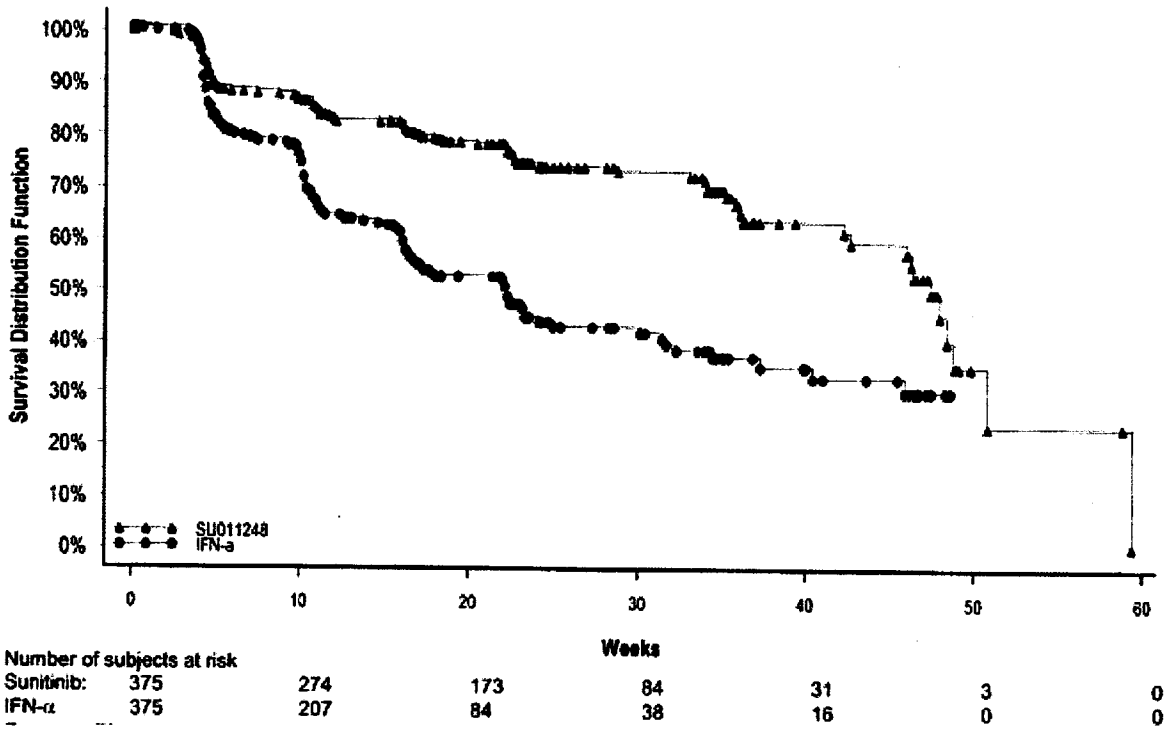
Yes. Please see Section *2.6, for analytical methods.*

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Figure 2 shows the Kaplan-Meier curve for progression-free survival for both groups of the study. In the primary analysis of PFS (core radiology assessment, ITT population), the median PFS on sunitinib was more than double that on IFN-a (47.3 vs 22.0 weeks).

Figure 2: Kaplan-Meier curve of progression-free survival by treatment (core radiology assessment, ITT population).



Median overall survival could not be determined because the data were not yet mature.
The following table shows the results for the efficacy endpoints of the study. There was a clear increased efficacy seen for sunitinib compared to IFN-a in the study.

Table 1: Summary of time-to-event endpoints – Core Radiology Assessment (ITT and AT Populations).

Variable	Number of Events: Sunitinib malate N (%)	IFN-a N (%)	Hazard Ratio	95% CI of Hazard Ratio	p-value
ITT population [N]	375	375			
PFS (events; n [%])	96 (25.6)	154 (41.1)	0.415	(0.320 to 0.539)	<0.000001
Median (weeks)	47.3	22.0			
95% CI	(42.6 to 50.7)	(16.4 to 24.0)			
TTP (events; n [%])	90 (24.0)	142 (37.9)	0.416	(0.318 to 0.545)	<0.000001
Median (weeks)	47.9	22.3			
95% CI	(45.9 to 50.7)	(17.3 to 31.3)			
AT population [N]	375	360			
PFS (events; n [%])	96 (25.6)	154 (42.8)	0.415	(0.320 to 0.539)	<0.000001
Median (weeks)	47.3	22.0			
95% CI	(42.6 to 50.7)	(16.4 to 24.0)			
TTP (events; n [%])	90 (24.0)	142 (39.4)	0.416	(0.318 to 0.545)	<0.000001
Median (weeks)	47.9	22.3			
95% CI	(45.9 to 50.7)	(17.3 to 31.3)			

Table 2: Summary of overall objective response rate – core radiology assessment (ITT and AT populations).

Variable	Treatment: Sunitinib malate N (%)	IFN-a N (%)	Treatment difference (%)	p-value
ITT population [N]	375	375		
ORR	103 (27.5)	20 (5.3)	22.13	<0.001
95% CI	(23.0 to 32.2)	(3.3 to 8.1)	(17.08 to 27.19)	
AT population [N]	375	360		
ORR	103 (27.5)	20 (5.6)	21.91	<0.001
95% CI	(23.0 to 32.3)	(3.4 to 8.4)	(16.81 to 27.01)	

The measure of exposure used in the exposure-response analyses was the combined (sunitinib+SU012662) steady-state AUC estimated from the CL from the sunitinib and metabolite population PK models. Due to the limited predictability of the covariate models for clearance, individual clearance estimates from the base model for sunitinib and SU012662 were used for calculating the AUC. As a result, only those subjects with PK data were included in the PK-PD analysis.

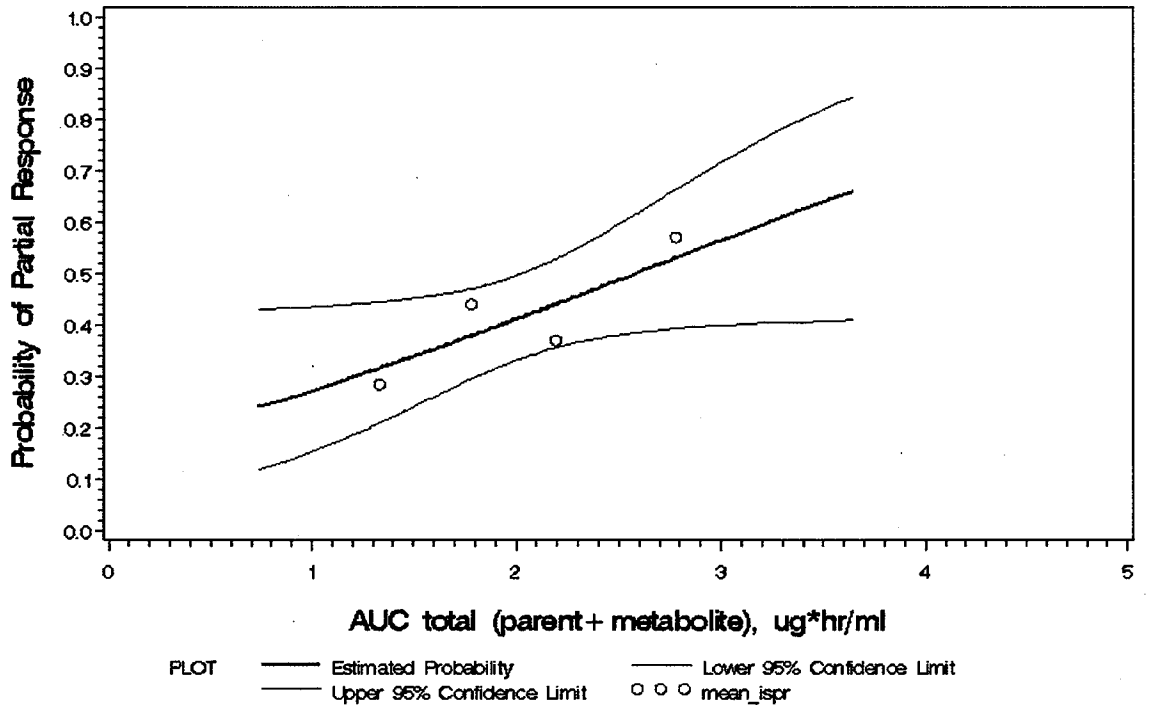
The combined AUC (sunitinib+SU012662) was chosen to reflect the contribution of the metabolite to the exposure of the active moieties. The metabolite is equipotent with the parent drug and has an AUC that is 20-30% of the parent drug. Using the sum of AUCs of the parent and metabolite would provide a more accurate measure of the exposure for evaluation of

exposure-response relationships. As the molecular weights of the parent drug and metabolite are similar (difference of one ethyl group), the mathematical sum of the AUCs was used instead of using the sum of the molar concentrations.
Consistent results were obtained for E-R relationships using only the parent drug AUC as the measure or exposure and using the combined parent+metabolite AUC as the measure of exposure.

The exposure-efficacy analysis was performed for three measures of efficacy: time to tumor progression or death, partial response rates and changes in tumor size. The data included both cytokine-refractory patients (studies 1006 and 014) as well as first-line treatment-naïve patients (study 1034). The data were limited to only patients with PK data, which resulted in the inclusion of only 42 patients from the phase 3 study. This confounded the findings and interpretation of results in treatment-naïve patients.

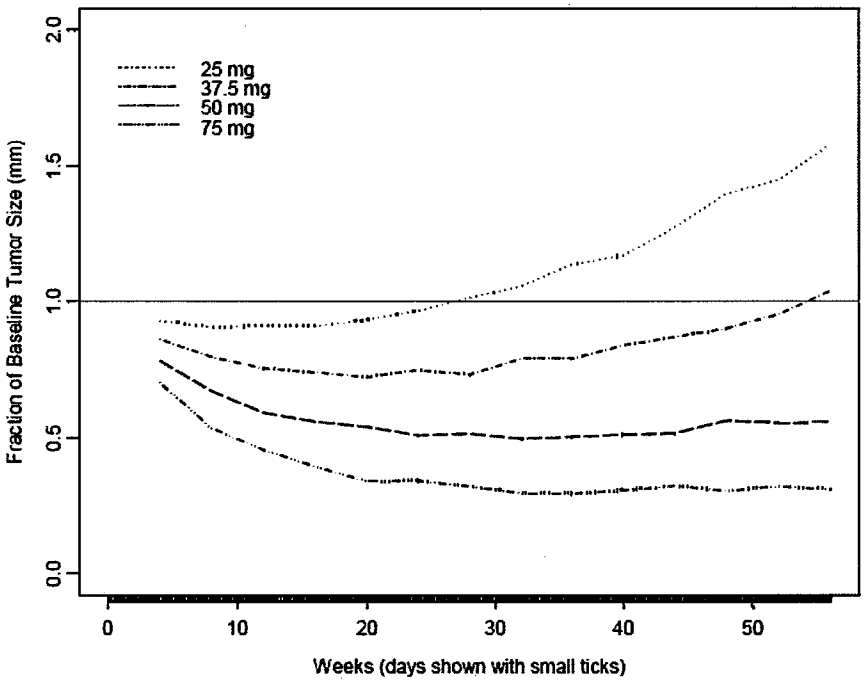
The Pharmacometrics report in the Appendix provides details of the data used, modeling methods and results. Briefly, there was no effect of AUC on time to tumor progression or death. This was probably due to the small number of patients with observed tumor progression or death in the first-line treatment-naïve patients. Analysis of response rates showed a significant correlation of AUC of sunitinib with the probability of a partial response in cytokine refractory patients (figure 3), suggesting a 1.9-fold increase in the probability of a PR with each unit increase in AUC.

Figure 3: Probability of partial responses vs. AUC total (sunitinib+SU012662) for second-line (cytokine-refractory) patients.



The tumor growth dynamics model provided a good description of changes in tumor size with sunitinib treatment. Line of therapy (treatment-naïve or cytokine refractory), baseline tumor size, sex and ECOG score were not significantly associated with changes in tumor size with sunitinib treatment. Using the model and assuming perfect patient compliance, simulation of tumor growth dynamics for the 50 mg QD (4/2 schedule) showed that 62% of patients would be classified as partial responders by RECIST criteria (i.e., 30% reduction in tumor volume).

Figure 4: Simulations showing the predicted population mean effect of different doses on the 4/2 schedule on tumor growth dynamics for sunitinib.



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

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

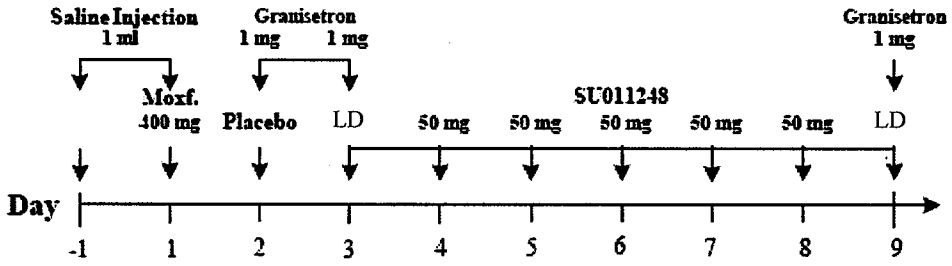
Please see the OCP review of the original NDA submission (August 2005) for details of the exposure-response analysis of the toxicity measures. Briefly, logistic regression was used to evaluate the relationship between exposure (AUC) and the observed frequency of severe grade 3/4 adverse events with exposure in GIST, MRCC and solid tumor patients. Significant relationships were seen with an increase in incidence of severe fatigue, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction dysfunction with exposure. No additional exposure-toxicity analyses were performed as part of the current submission.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The sponsor has conducted a study to fulfill a phase 4 commitment to evaluate the effect of sunitinib on QTc intervals in advanced solid tumor patients.
Please refer to the review by the CDER Interdisciplinary Review Team (IRT) for QT evaluation for details (submission dated 30-Mar-2006).

Study A6181005 was a single-blind study in 48 male and female patients, 18-75 years old, with advanced solid tumors. These patients had either failed standard therapy or had advanced malignanacies for which no standard acceptable therapy existed. The study design is displayed in figure 5.

Figure 5: Study design scheme for QTc study (A6181005)



Patients underwent serial electrocardiogram (ECG) assessments on Day -1, then received a single dose of moxifloxacin on Day 1 and a single dose of placebo on Day 2, followed by a 1-week course of SU011248 (loading dose (LD) on Days 3 and 9, maintenance dose on Days 4-8). In order to minimize the probability of inducing nausea and or vomiting, all subjects were pretreated with intravenous granisetron (1 mg) prior to dosing on Days 3 and 9. Granisetron was also administered to subjects on Day 2 (placebo only day) in order to assess its effect on ECG.

Two loading dose levels of sunitinib were evaluated in this study. The first group received 150 mg as the loading dose on day 3 and day 9, and the second group received 200 mg loading doses on days 3 and 9. The loading dose on day 3 was calculated to achieve the target concentration of 75-100 ng/ml, which was the range of concentrations achieved following the recommended dosage regimen of 50 mg QD on a 4/2 schedule (4 weeks on and 2 weeks off). The loading dose on day 9 was calculated to achieve target concentrations that were 2-fold higher (>180 ng/ml) than the therapeutic levels achieved on day 3. Loading doses of 150 mg and 200 mg were given on days 3 and 9. In addition, both groups received 50 mg QD, which is the recommended daily dose, as the maintenance dose on days 4, 5, 6, 7 and 8.

A total of 48 patients were enrolled in the study, with 47 patients receiving at least one dose of the drug on day 3 (Intent-to-treat or ITT **population, n=47). The "evaluable" population was** defined as the subjects who completed all dosing and all PK and ECG evaluations and whole combined (parent+metabolite) concentrations were above the target level of approximately 200 ng/ml (i.e., > 180 ng/ml) on day 9.

Demographics and other patient characteristics are summarized in *Table* 3.

Table 3. Summary of Demographic and Baseline Characteristics

Variable	ITT Population (N = 47)	Evaluable Population (N = 24)	Safety Analysis Population (N = 48)
Sex [n (%)]			
Male	25 (53)	9 (38)	25 (52)
Female	22 (47)	15 (62)	23 (48)
Race [n (%)]			
White	41 (87)	19 (79)	42 (88)
Asian	3 (6)	3 (13)	3 (6)
Not Listed	3 (6)	2 (8)	3 (6)
Age (years)			
Mean (std)	59.4 (14.8)	59.7 (13.1)	59.4 (14.6)
Median (range)	60.0 (20.0, 87.0)	61.0 (31.0, 79.0)	60.0 (20.0, 87.0)
< 65 [n (%)]	27 (57)	14 (58)	28 (58)
≥ 65 [n (%)]	20 (43)	10 (42)	20 (42)
Weight (kg)			
Mean (std)	72.9 (16.6)	73.3 (18.4)	72.4 (16.7)
Median (range)	76.7 (41.7, 119.3)	75.1 (41.7, 119.3)	75.1 (41.7, 119.3)
ECOG performance status [n (%)]			
0	13 (28)	6 (25)	13 (27.1)
1	34 (72)	18 (75)	35 (72.9)

This study was designed to test the null hypothesis that the QT/QTc prolongation is at least 10 ms versus the alternative hypothesis that the QT/QTc prolongation is less than 10 ms. The primary endpoint was the QTcF interval for Day 9, placebo-adjusted change from baseline, for the evaluable population. The sponsor compared two methods of baseline correction: a time-matched baseline correction using day -1 QTcF measurements and a within-day baseline correction using the pre-dose baseline value for each arm of the study.

The moxifloxacin arm of the study was used as an active control to establish that the study design had adequate sensitivity to detect a significant change in QTc. There were negligible changes in QTc on day 2 (placebo) with a maximum mean change in QTc of ≤ 2 msec. This indicates that the granisetron, given on day 2 had a negligible effect on the QTc interval.

Table 4 presents the maximum mean placebo-adjusted QTc changes from baseline observed after treatment with moxifloxacin (evaluable and ITT populations, using both baseline correction methods). As There were negligible changes in QTc on day 2 (placebo) with a maximum mean change in QTc of ≤ 2 msec. This indicates that the granisetron, given on day 2 had a negligible effect on the QTc interval.

Table shows, the maximum mean change obtained was > 5 msec with the 90% CI lower limit > 0, regardless of the population used.

There were negligible changes in QTc on day 2 (placebo) with a maximum mean change in QTc of ≤ 2 msec. This indicates that the granisetron, given on day 2 had a negligible effect on the QTc interval.

Table 4. Summary of Maximum Mean Placebo-Adjusted Changes from Baseline in QTcF and QTcS Following a Single Dose of 400 mg Moxifloxacin (Evaluable and ITT Populations)

Parameter	Population	Baseline Correction Method	N	Time (hr)	Maximum Mean Placebo-Adjusted Change from Baseline [a]	90% CI [*]
QTcF (msec)	Evaluable	Within-day	24	24	9.8	4.7, 14.9
QTcF (msec)	Evaluable	Time-matched	24	24	5.6	1.9, 9.3
QTcF (msec)	ITT	Within-day	46	4	9.0	5.3, 12.6
QTcF (msec)	ITT	Time-matched	47	24	5.5	3.4, 7.7
QTcS (msec)	Evaluable	Within-day	24	24	10.0	5.0, 15.0
QTcS (msec)	Evaluable	Time-matched	24	24	5.7	2.0, 9.4

[*] Means and 90% confidence intervals (CI) were computed from change from baseline data using ANCOVA models with terms of baseline, gender, and treatment.

Figure 6 shows the time course of placebo-adjusted QTcF changes from baseline following the day 3 and day 9 doses of sunitinib. Table displays a summary of the results for maximum mean changes from baseline in QTc following sunitinib on day 3 and day 9.

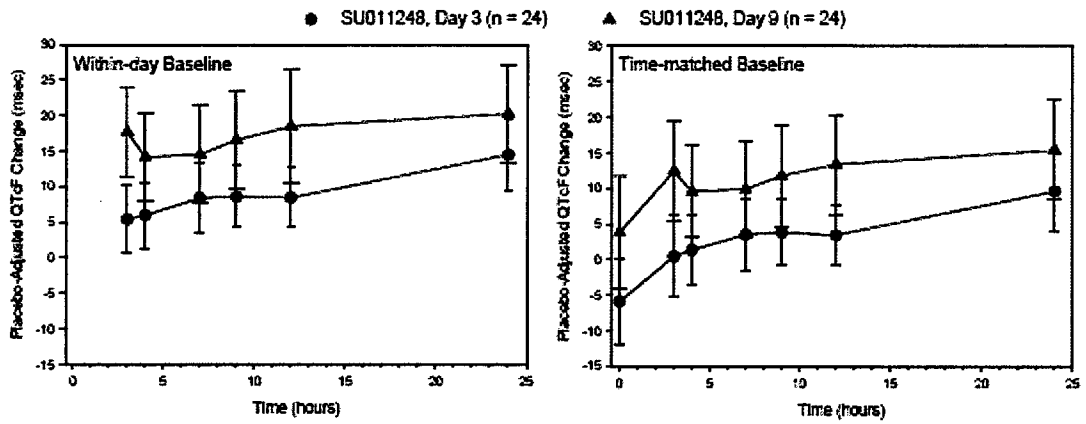
Table 5. Summary of Maximum Mean Placebo-Adjusted Changes from Baseline in QTcF and QTcS Following Dosing with Sunitinib – Day 3 and Day 9 – All Patients Combined (Evaluable and IT Populations).

Parameter	Population	Baseline Correction Method	N	Time (hr)	Maximum Mean Placebo-Adjusted Change from Baseline *	90% CI *
Day 3						
QTcF (msec)	Evaluable	Within-day	24	24	14.5	9.5, 19.5
QTcF (msec)	Evaluable	Time-matched	24	24	9.6	4.1, 15.1
QTcF (msec)	ITT	Within-day	47	24	11.9	8.6, 15.2
QTcF (msec)	ITT	Time-matched	47	24	6.9	3.3, 10.4
QTcS (msec)	Evaluable	Within-day	24	24	12.7	8.1, 17.3
QTcS (msec)	Evaluable	Time-matched	24	24	7.4	2.4, 12.5
Day 9						
QTcF (msec)	Evaluable	Within-day	24	24	20.3	13.4, 27.1
QTcF (msec)	Evaluable	Time-matched	24	24	15.4	8.4, 22.4
QTcF (msec)	ITT	Within-day	43	24	17.7	12.9, 22.6
QTcF (msec)	ITT	Time-matched	43	24	12.7	8.1, 17.3
QTcS (msec)	Evaluable	Within-day	24	24	19.2	12.3, 26.1
QTcS (msec)	Evaluable	Time-matched	24	24	13.9	7.0, 20.9

An effect on QTc (defined as a mean placebo-adjusted change of ≥ 10 msec with a 90% CI upper limit ≥ 15 msec) was observed on Day 3 using the within-day baseline correction method, and on Day 9 using both baseline correction methods (see table above). The maximum mean placebo-adjusted change from (within-day) baseline QTcF was 14.5 msec (90% CI: 9.5 – 19.5) at therapeutic levels of sunitinib (day 3) and was 20.3 msec (90% CI: 13.4 – 27.1) at supratherapeutic (2-fold higher than therapeutic) levels of sunitinib. The method of baseline correction did not markedly affect the shape of the QTc change versus time curves, though the magnitude of change was lower for the time-matched baseline correction method compared to the within-day correction (Figure 4).

The maximum mean changes in QTc occurred at the 24 hr time-point on both day 3 and day 9. Visual examination of the time course of QTc changes suggests a delay in the time of the peak effect relative to peak concentrations (Tmax ranged from 7 to 10 hrs).

Figure 6: Plot of Mean (90% CI) Placebo-Adjusted QTcF Changes from Baseline vs. Time for All Patients Combined (Evaluable Population)



There were 4 evaluable patients (all female) who showed QTc intervals > 450 msec and 6 ITT patients (5 female) who showed elevations in QTc > 450 msec. Changes in QTc (time-matched) between 30 and 60 msec occurred in 9 evaluable patients and changes in QTc > 60 msec was seen in 1 evaluable patient.

There were two loading dose groups included in the evaluable population, 150 mg (n=4) and 200 mg (n=20). Table displays the PK data obtained in the patients in the study. The average Cmax values on day 9 for both loading dose groups exceeded 200 ng/ml, indicating that supratherapeutic (approximately 2-fold) levels were achieved on day 9 in the sample.

Table 6. Summary of sunitinib (SU011248), metabolite (SU012662) and total drug (Sunitinib+SU012662) PK parameters by loading dose and study day (evaluable population).

Pharmacokinetic Parameters	Arithmetic Mean (CV %) [Median]			
	Loading Dose 150 mg (N = 4)		Loading Dose 200 mg (N = 20)	
	Day 3	Day 9	Day 3	Day 9
SU011248				
C_{max} (ng/mL)	91.0 (32) [82.7]	169 (32) [165]	137 (23) [127]	208 (26) [195]
T_{max} (hr) *	9.1 (7.5, 23.1)	10.6 (4.2, 12.4)	7.2 (3.3, 12.2)	7.4 (3.4, 11.9)
AUC_{0-24} (ng*hr/mL)	1650 (30) [1559]	3201 (33) [3367]	2255 (20) [2174]	3876 (28) [3601]
C_{trough} (ng/mL)	69.1 (41) [70.2]	133 (37) [144]	85.7 (27) [85.9]	148 (38) [135]
C_{max} Ratio (Day 9/Day 3)	NA	1.85 (10) [1.89]	NA	1.55 (20) [1.50]
AUC_{0-24} Ratio (Day 9/Day 3)	NA	1.93 (16) [1.99]	NA	1.72 (17) [1.75]
SU012662				
C_{max} (ng/mL)	30.9 (47) [32.6]	78.7 (33) [83.4]	28.3 (28) [30.7]	64.9 (37) [58.5]
T_{max} (hr) *	10.5 (7.5, 23.1)	10.6 (2.8, 23.8)	7.2 (3.3, 23.7)	7.4 (3.0, 24.1)
AUC_{0-24} (ng*hr/mL)	578 (53) [574]	1519 (30) [1553]	483 (28) [465]	1220 (36) [1140]
C_{trough} (ng/mL)	26.2 (43) [27.7]	69.6 (33) [74.9]	20.1 (36) [19.3]	49.6 (49) [41.6]
C_{max} Ratio (Day 9/Day 3)	NA	2.75 (23) [2.80]	NA	2.36 (30) [2.25]
AUC_{0-24} Ratio (Day 9/Day 3)	NA	2.98 (33) [2.96]	NA	2.57 (26) [2.49]
Total Drug				
C_{max} (ng/mL)	122 (30) [118]	243 (24) [239]	164 (22) [160]	271 (26) [262]
T_{max} (hr) *	10.5 (7.5, 23.1)	10.6 (4.2, 23.8)	7.2 (3.3, 12.2)	7.4 (3.1, 22.3)
AUC_{0-24} (ng*hr/mL)	2229 (27) [2178]	4720 (22) [4678]	2737 (20) [2669]	5096 (29) [5022]
C_{trough} (ng/mL)	95.3 (31) [98.3]	203 (26) [197]	106 (28) [108]	197 (40) [186]
C_{max} Ratio (Day 9/Day 3)	NA	2.03 (8) [2.03]	NA	1.67 (19) [1.70]
AUC_{0-24} Ratio (Day 9/Day 3)	NA	2.16 (16) [2.18]	NA	1.86 (16) [1.86]

N/A – not applicable.
* Median (min, max).

Exposure-Response Relationships: Figure 7 shows an overlay of the time courses of mean concentrations (for sunitinib, metabolite and combined drug) and mean placebo-adjusted QTcF change from baseline on day 3 and day 9. As the plots indicate, there was a delay in the QTcF change relative to the concentrations. Peak changes in QTcF occurred at 24 hrs while peak concentrations were achieved between 7 and 10 hrs.

The delta QTcF –time profiles for both days 3 and 9 appear to have peaked at the 24 hour time-point and for a few patients, it appeared to be further increasing (see Figure 7). For day 9 there were two additional timepoints where ECG was collected at 72 and 168 hours. For 3 patients on day 9 the QTc appeared to be higher at 72 and 168 hrs. We are unsure if the QTc may have peaked beyond the 24 hour timepoint. Given this observation, we would want to include the most conservative estimates in the label (i.e. the within-day correction on days 3 and 9). Also, the **sponsor's pre-specified endpoint** for the QTc study was the day 9, placebo corrected, within-day baseline corrected change in QTcF.

Figure 7: Overlay Plot of Mean Sunitinib, SU012662 and Combined Drug (Sunitinib+SU012662) Concentrations and Mean Placebo-Adjusted QTcF change from Baseline vs. Time for All Sunitinib Loading Dose Groups (Evaluable Population).

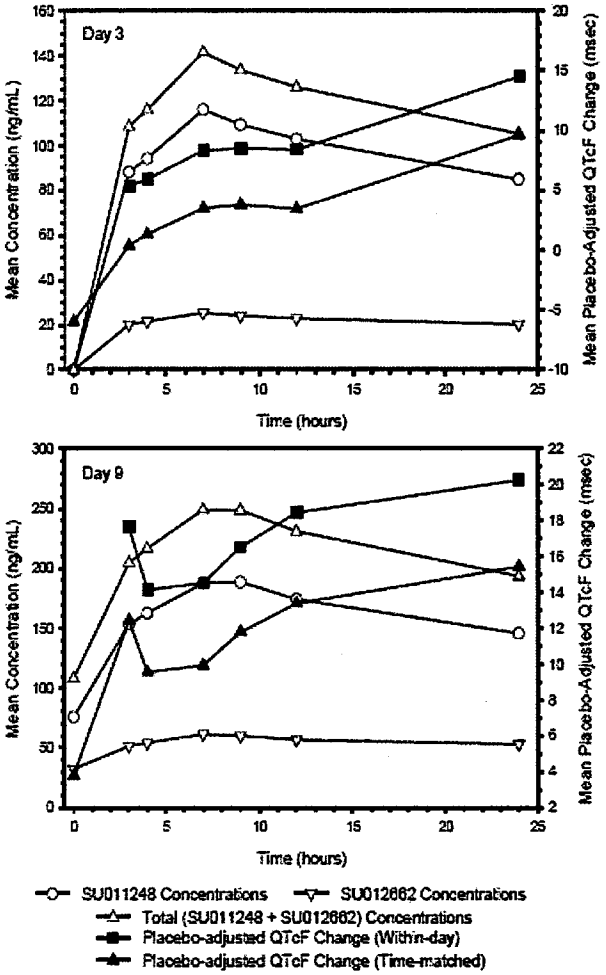
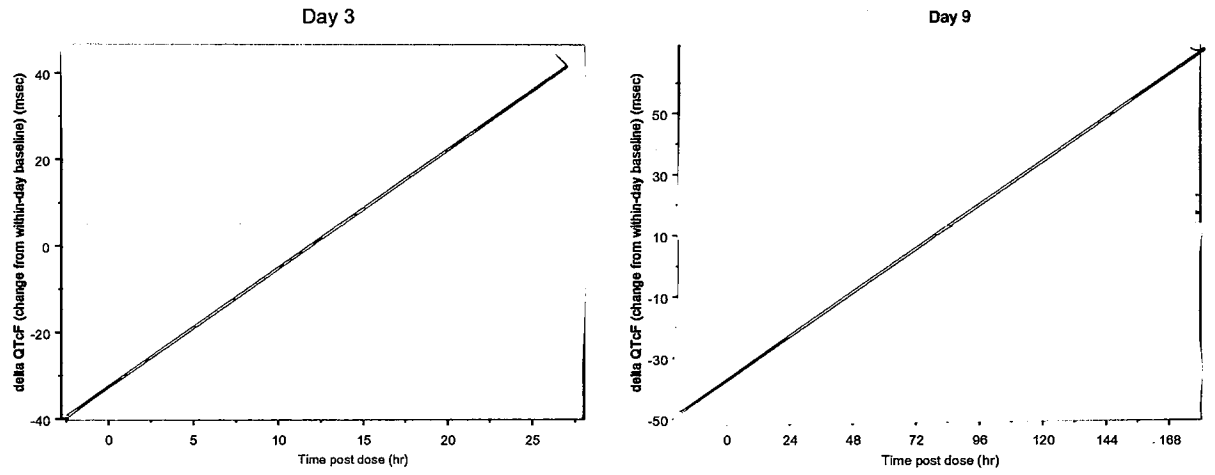


Figure 8: Individual Delta QTcF vs. Time Plots for All Patients on Day 3 (upper panel) and Day 9 (lower panel)

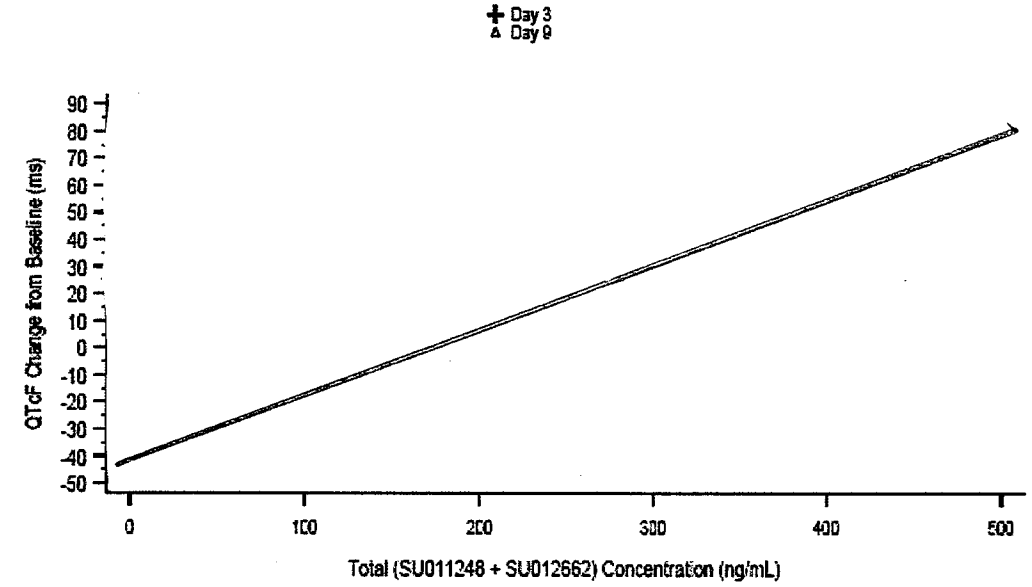


b(4)

The delay in peak QTc changes relative to concentration indicates a disequilibrium between concentration and effect. This is demonstrated by a counter-clockwise hysteresis in plots of concentration vs. QTc change, and this pattern was seen in over 50% of individuals in the study.

Figure 9 shows the scatter plots of placebo-adjusted QTcF change from baseline vs. combined sunitinib+SU012662 concentration. The plots suggest a positive association between change in QTcF and concentration. The sponsor indicated that mixed-effect modeling could not be conducted due to the disequilibrium between concentration and QTcF, which violates the assumption of the linear PK-QT model that was to be utilized for this analysis.

Figure 9: Scatter Plot of Individual Placebo-Adjusted QTcF Changes from Baseline vs. Total Drug (Sunitinib + SU012662) Concentrations (ITT population). Upper panel: Time-Matched Baseline-Correction. Lower panel: Within-day Baseline Correction.



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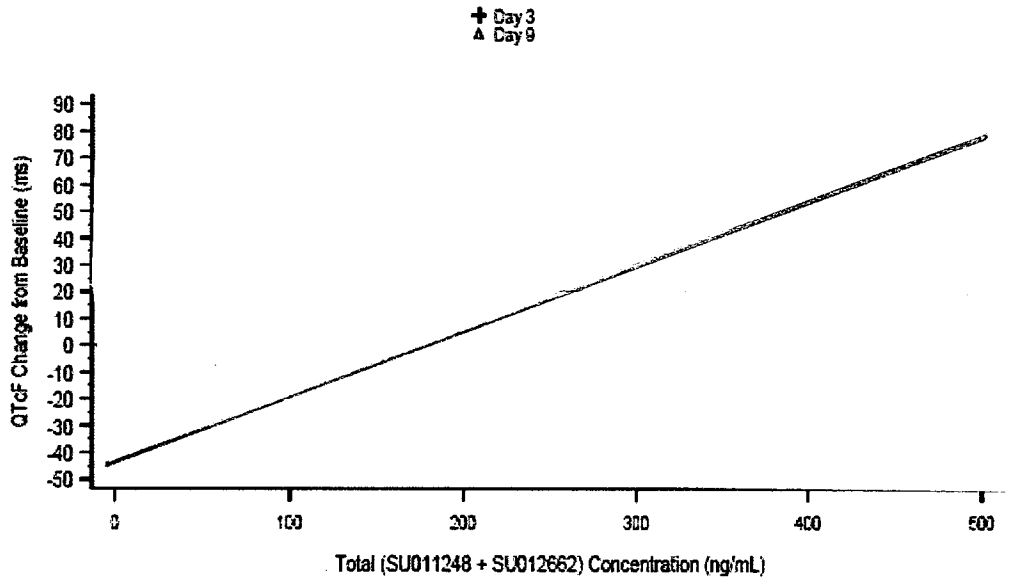


b(4)

In summary, administration of sunitinib to achieve therapeutic concentrations resulted in a 14.5 msec increase in the QTcF interval and supratherapeutic concentrations of sunitinib following the second loading dose resulted in a 20.3 msec increase in QTcF intervals.

Evaluation of QTc data from phase 3 study:
The sponsor submitted the results of their pivotal phase 3 study comparing sunitinib vs. interferon (IFN) in patients with advanced renal cell cancer. As part of this study, ECGs were done at screening (baseline) and then on day 28 (at trough).
Additional ECGs were done as indicated. QTc results (Fridericia's correction) and change from baseline are summarized by day in *Table* 7.

Table 7. QTc Interval and Change from Baseline in QTc by Day for Sunitinib (upper panel) and IFN (lower panel) – Study A6181034.

	Study Period	N	Mean	Std	Minimum	Median	Maximum
Sunitinib							
QTc (Fridericia) (msec)	Baseline	371	400.0	26.0	266.0	400.7	481.5
	Cycle 1 Day 28	341	408.2	27.6	242.5	406.7	524.8
	Cycle 2 Day 1	2	417.5	4.9	414.0	417.5	421.0
	Cycle 2 Day 28	1	393.9		393.9	393.9	393.9
	Termination	1	445.8		445.8	445.8	445.8
Change from Baseline in QTc (Fridericia) (msec)	Cycle 1 Day 28	337	8.0	23.7	-95.4	6.9	117.3
	Cycle 2 Day 1	2	17.7	17.2	5.5	17.7	29.9
	Cycle 2 Day 28	1	8.5		8.5	8.5	8.5
	Termination	1	39.2		39.2	39.2	39.2
IFN							
QTc (Fridericia) (msec)	Baseline	358	398.8	27.8	288.4	399.6	488.0
	Cycle 1 Day 28	312	403.2	27.0	297.1	404.1	473.6
	Cycle 2 Day 1						
	Cycle 2 Day 28						
	Termination	2	422.3	9.2	415.8	422.3	428.8
Change from Baseline in QTc (Fridericia) (msec)	Cycle 1 Day 28	311	3.8	24.2	-85.6	2.5	116.3
	Cycle 2 Day 1						
	Cycle 2 Day 28						
	Termination	2	24.2	3.8	21.5	24.2	26.9

There was a mean 8 msec (Std: 23.7, range: -95.4 to 117.3) increase in QTcF from baseline across the sample for sunitinib (n=337) and a 3.8 msec (Std: 24.2, range: -85.6 to 116.3) increase in QTcF from baseline for IFN (n=311).

Table summarizes the number of patients with various grades of QTc changes, as defined by NCI CTC version 3 (National Cancer Institute Common Toxicity Criteria, Bethesda, MD). The table indicates that 2.9% of sunitinib and 2.2% of IFN patients showed QTc between 470 and 500 msec or change in QTc greater than 60 msec.

Table 8. Number of Patients with Various Grades of QTc Changes in Sunitinib and IFN Arms of Study A6181034.

Grade	Sunitinib Total N=375	IFN Total N=360
Grade 0: QTc < 450 msec	321 (85.6%)	292 (81.1%)
Grade 1: QTc > 450 - 470 msec	10 (2.7%)	13 (3.6%)
Grade 2: QTc > 470 - 500 msec or deltaQTc > 60 msec	11 (2.9%)	8 (2.2%)
Grade 3/4: QTc > 500 msec	1 (0.3%)	0 (0.0%)
TOTAL	343 (91.5%)	313 (86.9%)

Based on the results of the QTc study, the Agency had the following recommendation with regard to ECG evaluation in future studies of sunitinib:

We believe that you have not reached the maximum QTc effect in your study. We recommend dthat you develop a ECG sampling plan to assess the maximum effect of the drug on the QTc interval as part of your current/future studies.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The phase 3 study for MRCC used only one dose level, i.e. 50 mg daily for 4 weeks of a 6-week cycle. This dose was selected primarily based on safety as dose-limiting toxicities were seen in the phase 1 studies at the next dose level of 75 mg. The phase 2 study of sunitinib in renal cell cancer patients also used the 50 mg dose and showed a 25-35% response rate for partial responses in MRCC patients. As there is no clinical effectiveness data at other dose levels, it is unclear if this dose level is optimal.

2.2.5 PK characteristics of the drug and its major metabolite

2.2.5.1 What are the single dose and multiple dose PK parameters?

Table 9 summarizes the PK parameters for sunitinib and SU012662 in oncology patients following multiple doses of sunitinib.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

There were no differences in the PK of sunitinib or SU012662 between healthy volunteers and patients. For details, please refer to OCP review of original NDA submission (August 2005).

Table 9: Summary of sunitinib and SU012662 PK parameters in oncology patients by study, following multiple doses of 50 mg QD sunitinib.

Table 40. Summary of Sunitinib and SU012662 PK Parameters in Oncology Patients Following Multiple Dosing With Sunitinib 50 mg QD (Studies 248-ONC-0511-002, RTKC-0511-005, RTKC-0511-013, and RTKC-0511-016)

Parameter	Mean (%CV)							
	Schedule 4/2				Schedule 2/2		Schedule 2/1	
	Study 002	Study 005		Study 013	Study 005	Study 013	Study 013	Study 016
	Day 28 (n = 8)	Day 14 (n = 15)	Day 28 (n = 10)	Day 28 (n = 5)	Day 14 (n = 14)	Day 14 (n = 6)	Day 14 (n = 5)	Day 14 (n = 12)
Sunitinib								
C_{max} (ng/mL)	72.2 (43)	90.2 (41)	82.4 (34)	68.5 (25)	92.5 (57)	56.7 (60)	66.8 (32)	91.9 (46)
AUC_{0-24} (ng*hr/mL)	1296 (47)	1697 (42)	1425 (34)	1262 (25)	1706 (52)	1035 (56)	1326 (35)	1592 (41)
T_{max} (hr)[a]	8.5 (3, 18)	6.1 (4.1, 12.3)	5.4 (0, 10.2)	4.1 (0, 8)	6.1 (2, 20)	6 (4, 8)	6 (4, 8)	6 (0, 8.3)
C_{trough} (ng/mL)	44.0 (59)	59.6 (51)	55.7 (40)	44.9 (40)	65.4 (58)	26.2 (66)	47.9 (36)	79.9 (54)
CL/F (L/hr)	46.4 (46)	N/A	40.7 (49)	41.4 (21)	37.9 (58)	61.5 (47)	44.4 (55)	41.0 (71)
SU012662								
C_{max} (ng/mL)	33.7 (73)	37.8 (25)	46.1(38)	37.8 (67)	32.3 (54)	18.3 (54)	22.7 (44)	25.1 (44)
AUC_{0-24} (ng*hr/mL)	592 (66)	731 (27)	844 (25)	667 (69)	640 (54)	362 (58)	485 (50)	477 (45)
T_{max} (hr)[a]	6.5 (3, 18)	6.1 (0, 10.1)	7.1 (0, 12)	6 (1, 8.1)	6 (0, 20)	5.1 (1, 8)	6 (3.9, 8)	6 (0, 24)
C_{trough} (ng/mL)	18.8 (45)	27.3 (27)	36.6 (50)	22.8 (69)	25.0 (62)	12.8 (64)	19.1 (54)	21.3 (50)
Total Drug								
C_{max} (ng/mL)	103 (47)	126 (33)	126 (34)	104 (33)	124 (51)	74.5 (53)	89.0 (30)	117 (43)
AUC_{0-24} (ng*hr/mL)	1888 (51)	2429 (35)	2264 (33)	1929 (39)	2351 (48)	1397 (52)	1810 (34)	2069 (39)
T_{max} (hr)[a]	9 (3, 18)	6 (4, 10)	5.5 (0, 10)	6 (1, 8.1)	6.5 (2, 20)	6 (4, 8)	6 (4, 8)	6 (0, 12)
C_{trough} (ng/mL)	62.9 (53)	86.8 (41)	92.3 (43)	67.7 (49)	90.3 (54)	39.0 (60)	67.0 (38)	101 (51)

Source: Appendix 2; Tables A-3.2.1.1 , A-3.2.1.2, A-3.2.1.3, A-3.2.2.1, A-3.2.2.2, A-3.2.2.3, A-3.2.3.1, A-3.2.3.2, and A-3.2.3.3.
%CV = % Coefficient of Variation; AUC_{0-24} = Area Under the Plasma Concentration Time Curve From 0 to 24 Hours; C_{max} = Maximum Concentration; C_{trough} = Plasma Concentration at Predose, 24, or 48 Hours Postdose; CL/F = Oral Clearance; T_{max} = Time to Maximum Concentration.
Note: All data presented are from Cycle 1.
[a] Values presented are median (min, max).

2.2.5.3 What are the characteristics of drug absorption?

Absorption of sunitinib following oral administration occurred with a median Tmax of 6 to 12 hours following single and multiple doses. SU012662 levels peaked at approximately the same time as sunitinib. For details, please refer to OCP review of original NDA submission (August 2005).

2.2.5.4 What are the characteristics of drug distribution?

Binding of sunitinib and its primary active metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration dependence in the range of 100 – 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25 - 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose. For details, please refer to OCP review of original NDA submission (August 2005).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

In a human mass balance study of [^{14}C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor

metabolites were identified in urine and feces but generally not found in plasma. For details, please refer to OCP review of original NDA submission (August 2005).

2.2.5.6 What are the characteristics of drug metabolism?

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

2.2.5.7 What are the characteristics of drug excretion?

Fecal excretion is the major route of elimination of sunitinib. Over a 21-day collection period, total recovery of radioactivity averaged 77±8.8%, with 61±7.2% in the feces and 16±2.5% in urine. Sunitinib was the primary species identified in feces and urine, followed by SU012662. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%. Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK of sunitinib and its primary metabolite SU012662 were found to be dose-proportional in the dose range of 25 to 100 mg. For details, please refer to OCP review of original NDA submission (August 2005).

2.2.5.9 How do the PK parameters change with time following chronic dosing?

With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma **concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL.** No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The variability in PK parameters in healthy subjects ranged from 15-36% for Cmax and AUC and 21-35% for apparent clearance of sunitinib. The estimates of variability in patients were higher, ranging from 25-60% for Cmax and AUC and 21-71% for apparent clearance. This represents a moderate range of variability.
For details, please refer to OCP review of original NDA submission (August 2005).

2.3. INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of several intrinsic factors was evaluated as part of the population PK analysis conducted at the time of the original review. In the current submission, the effect of hepatic impairment on sunitinib PK was evaluated. This was one of the post-marketing commitments made by the applicant at the time of the original NDA submission.

Hepatic Impairment:
The effect of hepatic impairment on sunitinib and SU012662 PK has been evaluated in study A6181079. The objectives of this study were to evaluate the effects of mild and moderate impaired hepatic function on the single-dose pharmacokinetics of sunitinib and its active metabolite, SU012662, and to assess the safety and tolerability of a single dose of sunitinib in subjects with mild and moderate impaired hepatic function

This was an open-label, single-dose, parallel-group study in three groups of subjects (8 subjects per group) with the following degrees of hepatic function:
Group 1: subjects with normal hepatic function
Group 2: subjects with mild hepatic impairment (Child-Pugh classification A, score 5-6)
Group 3: subjects with moderate hepatic impairment (Child-Pugh classification B, score 7-9).

All subjects in all groups received a single 50-mg dose of sunitinib. Serial blood samples were collected for analysis of sunitinib and SU012662 levels at baseline (predose) and 1, 2, 4, 6, 8, 12, 16, 24 (Day 2), 36 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7) hours after dosing. Additional samples were collected during follow-up visits on days 9, 11, 13, 15, 17, and 21.
A separate larger quantity of blood (10 mL) for the measurement of SU011248 and SU012662 protein binding was collected at 0 hour and at 6 hours after dosing.

PK parameters were estimated for sunitinib and SU012662 for each individual using non-compartmental methods. Both total and unbound exposures (Cmax, AUC) were estimated. Parameters were compared across groups using ANOVA.

Results: Table 10 shows the demographics of the 3 groups of subjects:

Table 10. Demographics and baseline characteristics of the subjects.

Characteristic	Healthy	Mild Impairment	Moderate Impairment
	n = 8	n = 8	n = 8
Male:Female	5:3	4:4	7:1
Age, years			
Mean (SD)	57.4 (5.3)	59.4 (7.4)	57.8 (8.9)
Range	53-70	50-73	48-78
Race, n			
White	7	8	6
Black	0	0	2
Asian	1	0	0
Weight, kg			
Mean (SD)	78.8 (19.4)	79.1 (14.3)	86.6 (20.4)
Range	52.0-109.0	51.7-98.9	51.7-112.9
Body Mass Index			
Mean (SD)	26.6 (5.2)	29.3 (4.8)	29.6 (5.7)
Range	20.0-36.0	18.4-34.2	19.6-35.7
Height, cm			
Mean (SD)	171.9 (8.9)	164.5 (8.1)	170.5 (9.6)
Range	163.0-187.0	157.5-177.8	154.9-182.9

One subject (Subject 10021030; normal hepatic function) had SU011248 and SU012662 concentrations that were very low or BLQ over the entire PK sampling period. This subject had an episode of emesis soon after dosing, which was reported as an AE. Data for this subject was excluded from analysis.

Table 11 shows the PK parameters for the sunitinib, SU012662 and for combined drug (sunitinib+SU012662), for the 3 hepatic impairment groups.

Table 11: PK parameters for sunitinib, SU012662 and combined drug for normal, mild and moderate hepatic impairment groups.

Parameter	Geometric Mean (95% Confidence Interval)		
	Normal N=7	Mild N=8	Moderate N=8
SU011248 Total			
AUC_{inf} (ng·h/mL)	1368.7 (1242.7, 1507.5)	1514.2 (1369.2, 1674.6)	1477.2 (1431.0, 1524.8)
AUC_{last} (ng·h/mL)	1354.8 (1228.8, 1493.7)	1484.6 (1344.8, 1639.0)	1454.7 (1408.3, 1502.5)
C_{max} (ng/mL)	21.9 (19.9, 24.0)	23.3 (22.2, 24.4)	22.7 (21.4, 24.0)
T_{max} (h)[a]	8.1 (6.0, 16.0)	8.0 (4.0, 12.0)	10.0 (1.0, 16.0)
$t_{1/2}$ (h)	63.8 (61.7, 65.9)	79.5 (75.3, 83.9)	79.2 (73.9, 84.9)
CL/F (L/h)	36.5 (33.2, 40.2)	33.0 (29.9, 36.5)	33.8 (32.8, 34.9)
SU011248 Unbound			
Fu (%)	9.8 (9.6, 10.1)	8.0 (7.7, 8.4)	9.0 (8.8, 9.2)
$AUC_{inf,u}$ (ng·h/mL)	134.5 (124.3, 145.5)	121.3 (111.5, 131.9)	132.7 (128.2, 137.4)
$AUC_{last,u}$ (ng·h/mL)	133.1 (122.9, 144.2)	118.9 (109.6, 129.0)	130.7 (126.3, 135.2)
$C_{max,u}$ (ng/mL)	2.2 (2.0, 2.3)	1.9 (1.8, 2.0)	2.0 (1.9, 2.1)

SU012662 Total			
AUC_{inf} (ng·h/mL)	559.4 (517.8, 604.4)	491.9 (459.7, 526.3)	505.1 (461.4, 552.9)
AUC_{last} (ng·h/mL)	530.7 (489.8, 575.0)	456.4 (428.5, 486.1)	475.0 (432.0, 522.3)
C_{max} (ng/mL)	4.3 (4.0, 4.7)	4.3 (4.0, 4.7)	4.3 (3.7, 5.0)
T_{max} (h)[a]	6.1 (6.0, 12.0)	6.0 (4.0, 48.0)	6.0 (1.0, 36.0)
$t_{1/2}$ (h)	110.9 (107.1, 114.7)	121.9 (114.4, 129.8)	112.6 (107.4, 118.1)
SU012662 Unbound			
Fu (%)	16.0 (15.5, 16.6)	13.5 (13.0, 14.1)	15.6 (15.4, 15.7)
$AUC_{inf,u}$ (ng·h/mL)	89.7 (82.8, 97.2)	66.6 (62.6, 70.9)	78.6 (72.1, 85.7)
$AUC_{last,u}$ (ng·h/mL)	85.1 (78.4, 92.3)	61.8 (58.2, 65.6)	73.9 (67.5, 81.0)
$C_{max,u}$ (ng/mL)	0.7 (0.6, 0.8)	0.6 (0.5, 0.6)	0.7 (0.6, 0.8)
Total Drug*			
AUC_{inf} (ng·h/mL)	1937.8 (1784.4, 2104.4)	2001.9 (1828.4, 2191.9)	1999.1 (1940.5, 2059.4)
AUC_{last} (ng·h/mL)	1912.6 (1759.9, 2078.4)	1956.1 (1794.1, 2132.7)	1958.4 (1896.8, 2022.0)
C_{max} (ng/mL)	26.0 (23.8, 28.5)	27.3 (26.0, 28.7)	26.7 (25.0, 28.6)
T_{max} (h)[a]	6.1 (6.0, 12.0)	8.0 (4.0, 12.0)	8.0 (1.0, 16.0)

Figure 10 shows the median concentration vs. time profiles for the three groups.

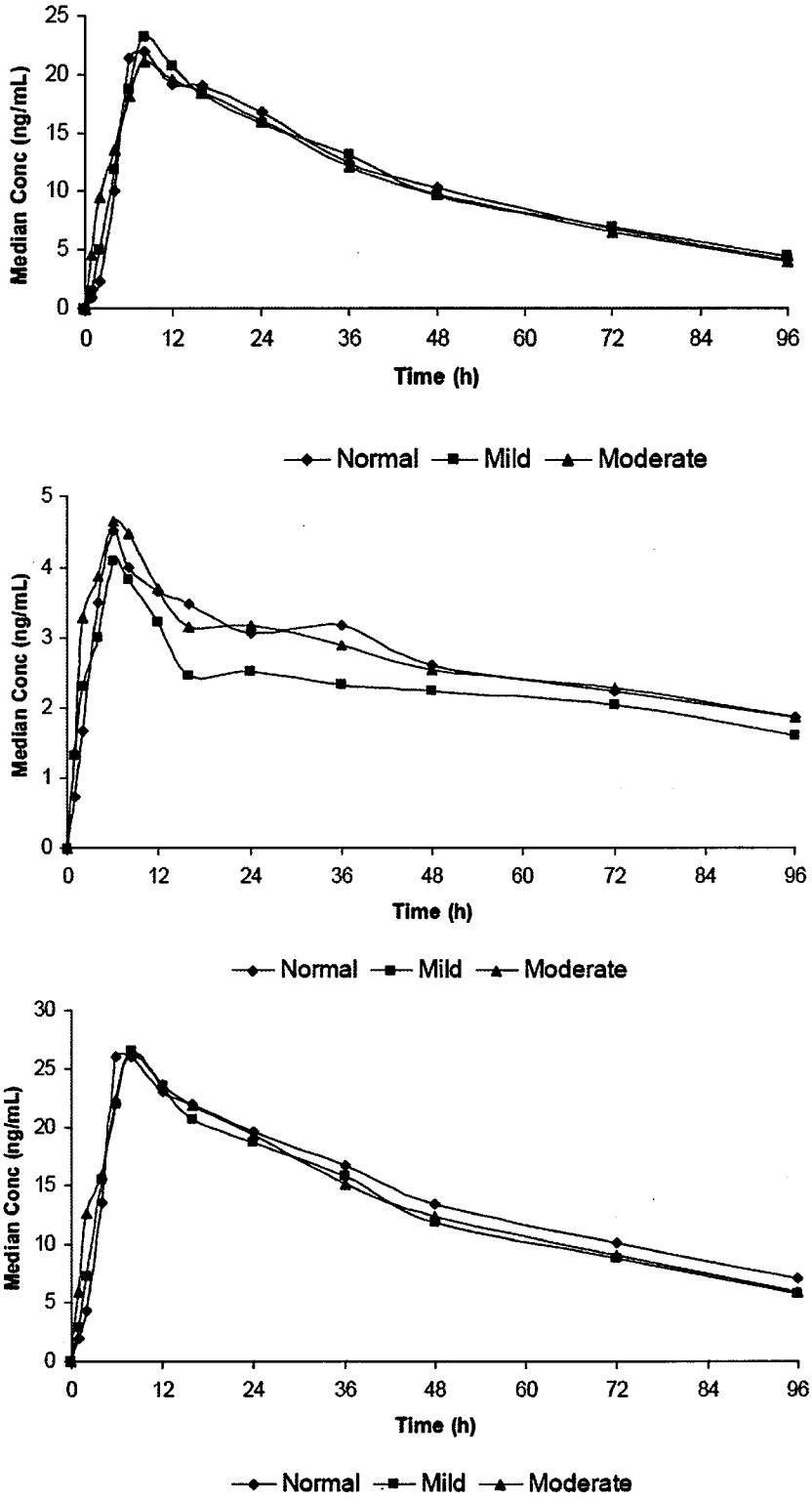
Statistical analysis revealed no differences in PK parameters among the three groups. Pairwise comparisons demonstrated that systemic exposure (AUCinf, AUClast and Cmax) of SU011248, SU012662, and Combined Drug was not significantly changed in subjects with mild and moderate hepatic impairment, compared with normal subjects.

The AUC ratios for sunitinib were 1.11 and 1.08 for the mild and moderate groups indicating an 8% to 11% increase in exposure to sunitinib. The AUC ratios for SU012662 were 0.88 and 0.90 indicating a 10% to 12% decrease in exposure to SU012662. These effects canceled each other out such that the AUC ratios for the Combined Drug were 1.03 for both impairment groups. This indicates that there was no net effect of hepatic impairment on sunitinib exposure.

Point estimates of the geometric mean ratio (mild/normal and moderate/normal) for SU011248 apparent clearance and half-life fell within the 80% to 125% range. The CL/F of SU011248 was not significantly different in subjects with hepatic impairment (33.0 L/h-33.8 L/h) compared with normal subjects (36.5 L/h).

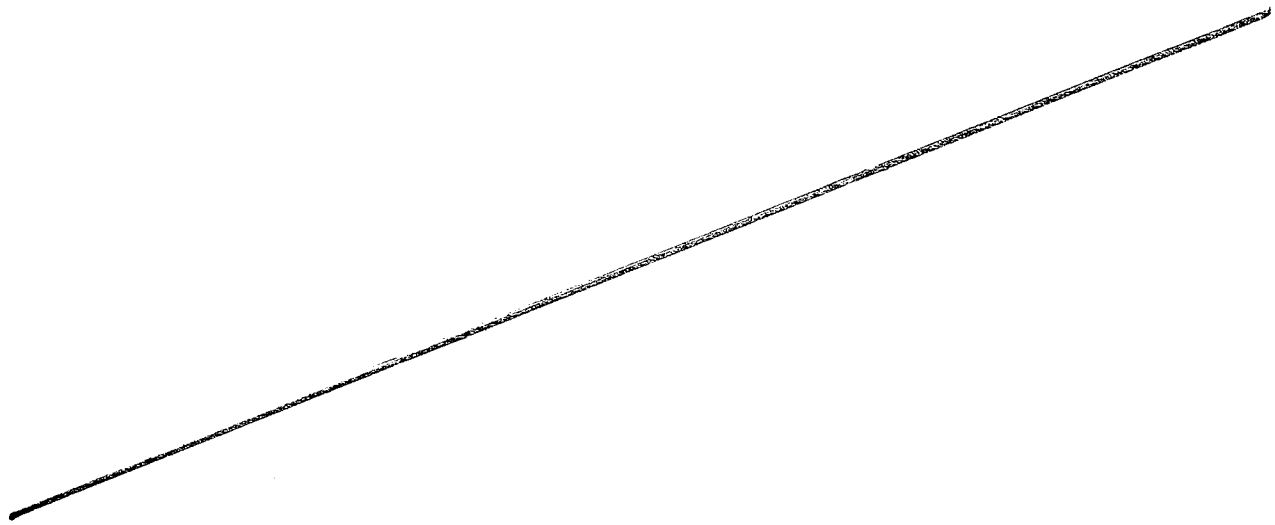
The unbound fractions of SU011248 and SU012662 were slightly smaller in the hepatically-impaired groups, compared with the normal group. For SU011248, the unbound fraction in the hepatic-impaired groups was 8.0% to 9.0 %, compared with 9.8% in the normal group. For SU012662, the unbound fraction in the hepatic-impaired groups was 13.5% to 15.6%, compared with 16.0% in the normal group. These differences between groups in protein binding were not statistically significant.

Figure 10: Median sunitinib concentration vs. time for normal, mild and moderate hepatic impairment groups. Upper panel: sunitinib, Middle panel: SU012662 and Lower panel: combined drug (sunitinib+SU012662).



To further explore the relationship between measures of hepatic impairment and sunitinib and SU012662 exposure, the AUC of sunitinib and SU012662 (total and unbound) was plotted as a function of albumin concentrations and as a function of bilirubin concentrations. As the following figures shows, there was no trend for any relationship between sunitinib and SU012662 exposure and these measures of hepatic function.

Figure 11: Scatter-plots of sunitinib AUC and sunitinib unbound AUC vs. Albumin (upper panels) and SU012662 AUC and SU012662 unbound AUC vs. Albumin (lower panels).



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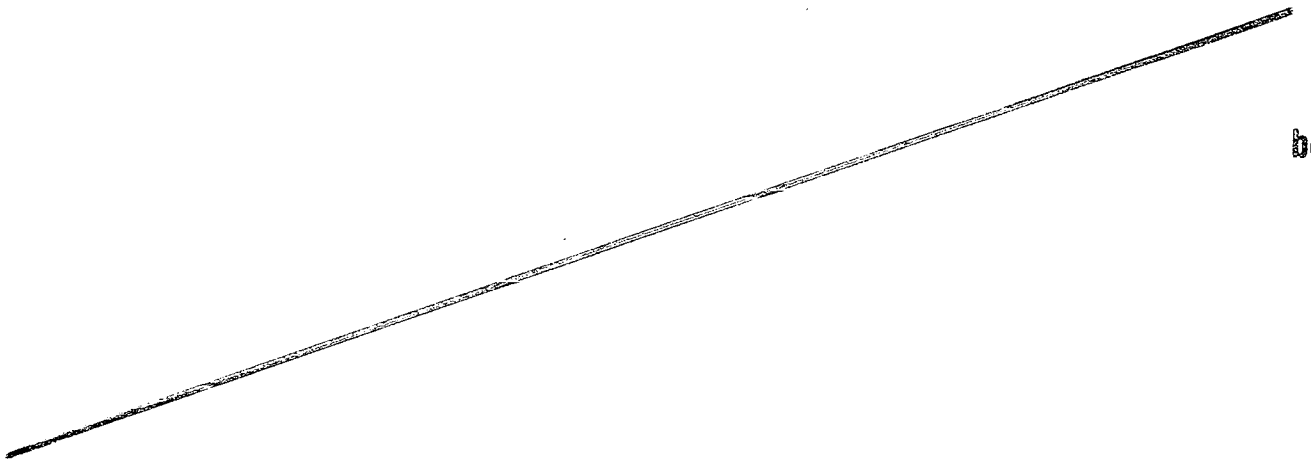

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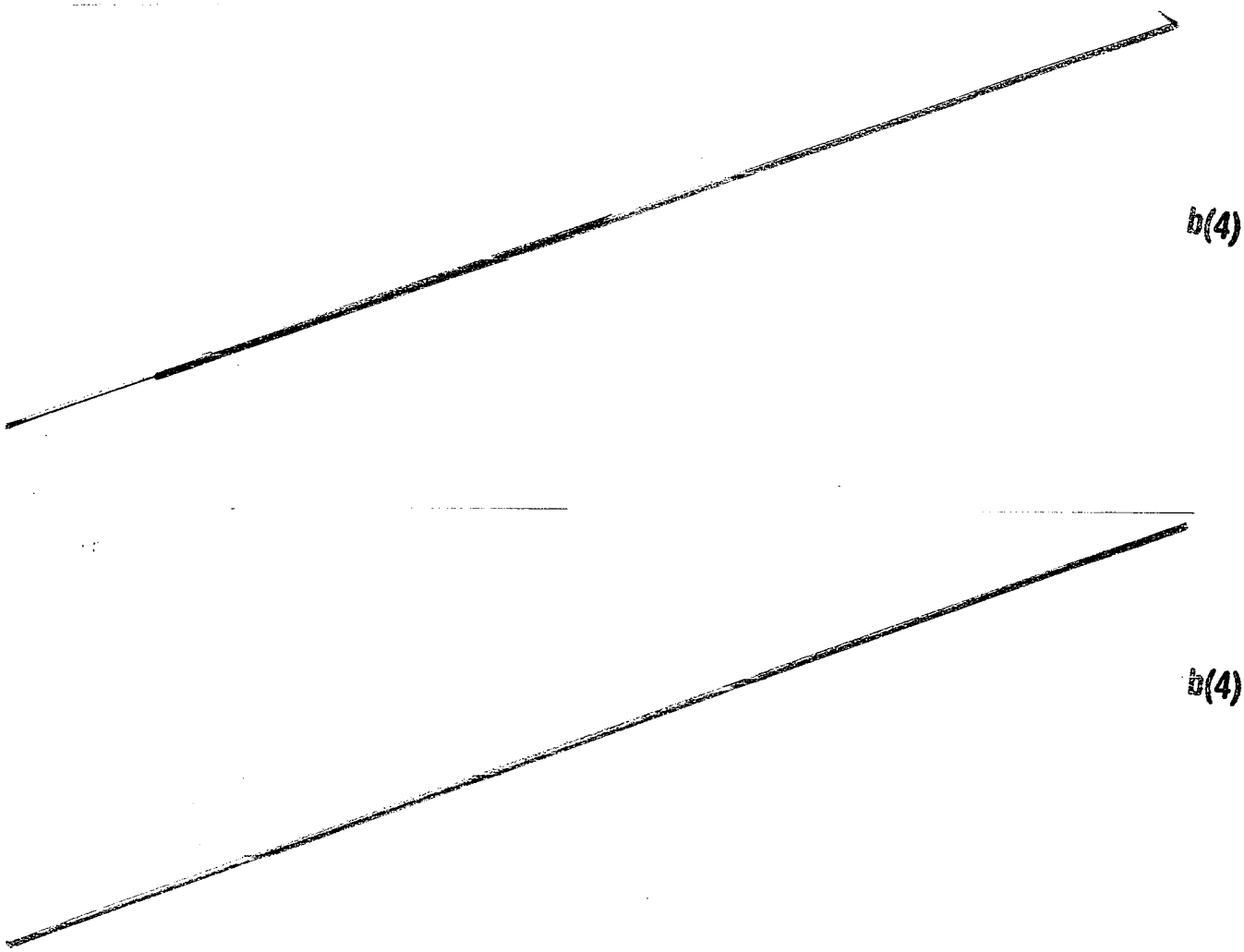
Figure 12: Scatter-plots of sunitinib AUC and sunitinib unbound AUC vs. Bilirubin (upper panels) and SU012662 AUC and SU012662 unbound AUC vs. Bilurubin (lower panels).



In summary, mean Cmax and AUC for sunitinib and SU012662 were similar between subjects with hepatic impairment and normal subjects. There was no effect of hepatic impairment on protein binding of sunitinib or SU012662 resulting in a lack of differences for unbound sunitinib and SU012662 exposures between hepatic impairment subjects and normal subjects. Thus, sunitinib dosing adjustments are not necessary for patients with mild to moderate hepatic impairment.

Table 12: Geometric mean ratios for sunitinib, SU012662 and combined drug in mild/normal and moderate/normal groups.

Parameter	Geometric Least Squares Mean Ratio (90% Confidence Interval)	
	Mild/ Normal	Moderate/ Normal
SU011248 Total		
AUC_{inf} (ng·h/mL)	1.11 (0.84, 1.47)	1.08 (0.81, 1.43)
AUC_{last} (ng·h/mL)	1.10 (0.83, 1.45)	1.07 (0.81, 1.42)
C_{max} (ng/mL)	1.06 (0.85, 1.34)	1.04 (0.82, 1.30)
T_{max}[a] (h)	0.35 (0.73)	-0.23 (0.82)
$t_{1/2}$ (h)	1.25 (1.03, 1.51)	1.24 (1.02, 1.51)
CL/F (L/h)	0.90 (0.68, 1.20)	0.93 (0.70, 1.23)
SU011248 Unbound		
Fu (%)	0.82 (0.73, 0.92)	0.91 (0.81, 1.03)
$AUC_{inf,u}$ (ng·h/mL)	0.90 (0.71, 1.14)	0.99 (0.78, 1.25)
$AUC_{last,u}$ (ng·h/mL)	0.89 (0.71, 1.13)	0.98 (0.78, 1.24)
$C_{max,u}$ (ng/mL)	0.87 (0.71, 1.07)	0.95 (0.77, 1.17)
SU012662 Total		
AUC_{inf} (ng·h/mL)	0.88 (0.67, 1.16)	0.90 (0.69, 1.19)
AUC_{last} (ng·h/mL)	0.86 (0.65, 1.14)	0.90 (0.68, 1.18)
C_{max} (ng /mL)	1.00 (0.67, 1.48)	0.99 (0.66, 1.46)
T_{max}[a] (h)	2.16 (0.03)	0.70 (0.48)
$t_{1/2}$ (h)	1.10 (0.92, 1.31)	1.02 (0.85, 1.21)
SU012662 Unbound		
Fu (%)	0.84 (0.76, 0.94)	0.97 (0.87, 1.09)
$AUC_{inf,u}$ (ng·h/mL)	0.74 (0.57, 0.97)	0.88 (0.67, 1.14)
$AUC_{last,u}$ (ng·h/mL)	0.73 (0.55, 0.95)	0.87 (0.66, 1.14)
$C_{max,u}$ (ng/mL)	0.84 (0.56, 1.26)	0.96 (0.64, 1.43)
Total Drug (SU011248 + SU012662)		
AUC_{inf} (ng·h/mL)	1.03 (0.80, 1.33)	1.03 (0.80, 1.32)
AUC_{last} (ng·h/mL)	1.02 (0.80, 1.31)	1.02 (0.80, 1.31)
C_{max} (ng/mL)	1.05 (0.83, 1.33)	1.03 (0.81, 1.30)
T_{max}[a] (h)	-0.29 (0.77)	-0.52 (0.60)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Not applicable.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

Not applicable. The applicant did submit a proposed pediatric study request (PPSR) in November 2005, and the Agency has issued a Written Request for pediatric studies to the applicant for the evaluation of sunitinib in pediatric malignancies.

2.3.2.3 Gender
Not applicable.

2.3.2.4 Race
Not applicable.

2.3.2.5 Renal impairment
No recommendations at this time. The applicant is conducting a study evaluating the pharmacokinetics of sunitinib in patients with renal impairment.

2.3.2.6 Hepatic impairment
The mean Cmax and AUC for sunitinib and SU012662 were similar between subjects with hepatic impairment and normal subjects. There was no effect of hepatic impairment on protein binding of sunitinib or SU012662 resulting in a lack of differences for unbound sunitinib and SU012662 exposures between hepatic impairment subjects and normal subjects. Thus, sunitinib dosing adjustments are not necessary for patients with mild to moderate hepatic impairment.

2.3.2.7 What pregnancy and lactation use information is there in the application?
None.

2.3.2.8 What pharmacogenetics information is there in the application and is it important or not?
None.

2.4. EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of sunitinib.

2.4.2 Drug-drug interactions

Please refer to the original NDA review for drug-drug interaction studies of sunitinib with CYP inhibitors and inducers.

2.5 GENERAL BIOPHARMACEUTICS

There were no biopharmaceutics issues in the current submission.
Please see original NDA review for information regarding the biopharmaceutics of this drug.

2.6 ANALYTICAL SECTION

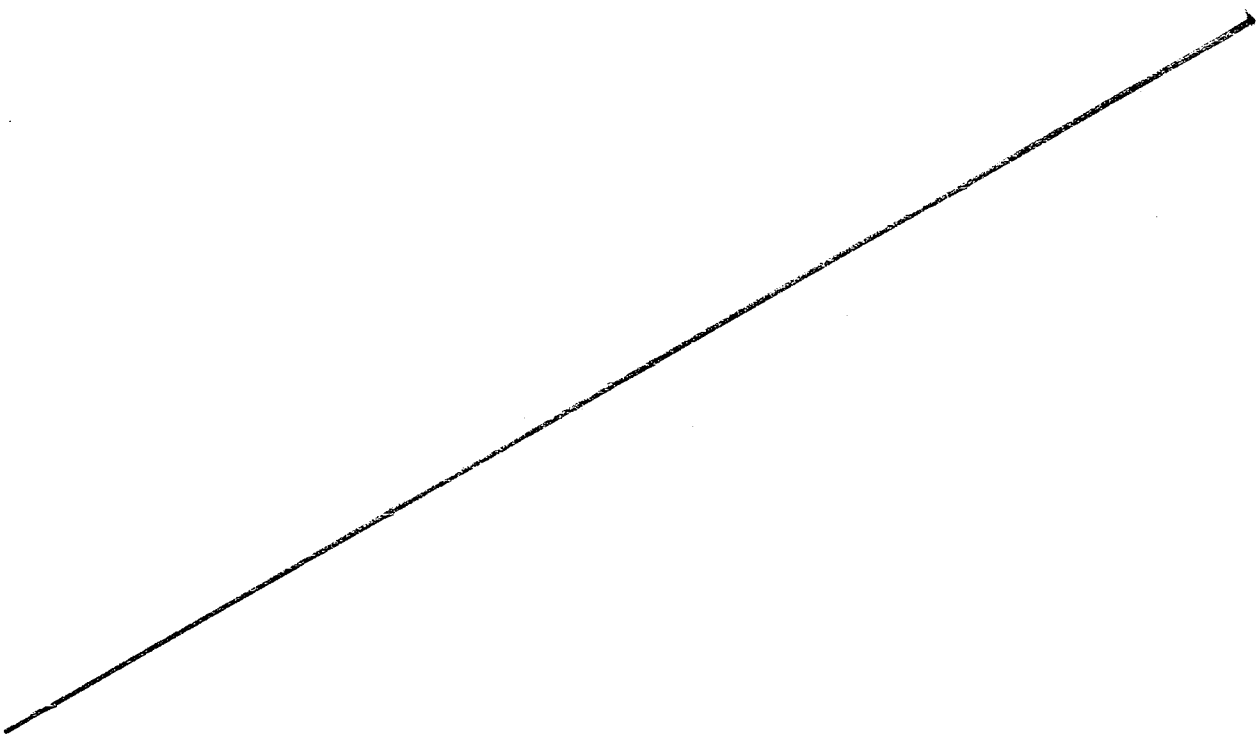
2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology studies?

Yes, in the hepatic impairment and QTc study, the parent compound, sunitinib and SU012662, the major metabolite were measured since these were the only two compounds found in the blood or urine.

2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis for that decision, and is it appropriate?

The parent compound and its active metabolite SU012662 as well as a minor metabolite SU12487 were selected for analysis. All three compounds were measured as free moieties detected by mass spectrometry.

2.6.3 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?



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13 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__√__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 2

4. INDIVIDUAL STUDY REVIEWS

Protocol Title: A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects With Impaired Hepatic Function

Protocol Number: A6181079

Study Objective(s): The objectives of this study were as follows:

- To evaluate the effects of mild and moderate impaired hepatic function on the single-dose pharmacokinetics of SU011248 and its active metabolite, SU012662.
- To assess the safety and tolerability of a single dose of SU011248 in subjects with mild and moderate impaired hepatic function.

METHODS

Study Design: This was an open-label, single-dose, parallel-group study. Volunteers were screened for participation within 14 days before the first dose of study medication. Three groups of subjects (8 subjects per group) with the following degrees of hepatic function were enrolled in the study:
Group 1: subjects with normal hepatic function,
Group 2: subjects with mild hepatic impairment (Child-Pugh classification A, score 5-6),
Group 3: subjects with moderate hepatic impairment (Child-Pugh classification B, score 7-9).
All subjects in all groups received a single 50-mg dose of SU011248.

Study Treatment: Subjects were admitted to the study unit 1 or 2 days before dosing (Day –1 or Day 0) and were confined in the study unit until Day 7. All subjects received a single dose of SU011248 on the morning of Day 1. Serial PK blood samples (4 mL at each time point) for the measurements of SU011248 and SU012662 were collected within 15 minutes before dosing (0 hour) and at 1, 2, 4, 6, 8, 12, 16, 24 (Day 2), 36 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7) hours after dosing. A separate larger quantity of blood (10 mL) for the measurement of SU011248 and SU012662 protein binding was collected at 0 hour and at 6 hours after dosing. Subjects were discharged from the study unit on Day 7 and returned to the study unit on Days 9, 11, 13, 15, 17, and 21 for additional PK blood sample collections. A single PK sample was collected at each visit, and the exact collection date and time was recorded.

Pharmacokinetic Evaluations:
Primary PK endpoint:

- SU011248 area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}), area under the plasma concentration-time curve from zero to time of last measurable concentration (AUC_{last}), and maximum observed plasma concentration (C_{max}).

Secondary PK endpoints:

- SU011248 time to first occurrence of C_{max} (T_{max}), terminal phase plasma half-life ($t_{1/2}$), apparent oral clearance (CL/F), apparent volume of distribution (V_z/F), fraction of drug

unbound in plasma (F_u), unbound AUC_{inf} ($AUC_{inf,u}$), unbound AUC_{last} ($AUC_{last,u}$), and unbound C_{max} ($C_{max,u}$)

- SU012662 AUC_{inf}, AUC_{last}, C_{max}, T_{max}, $t_{1/2}$, F_u, $AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$.

Safety Evaluations: To assess safety, physical examinations and 12-lead ECGs were performed, vital signs and AEs were monitored, and clinical laboratory tests were conducted.

Statistical Methods: Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, were provided for continuous endpoints. The number and percent of patients in each category were provided for categorical variables.
For qualitative parameters, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the parameter were presented.
Quantitative parameters were summarized by presenting the population size, mean, standard deviation, CV%, median, minimum, and maximum values.

In general, data were presented by study group (i.e., Group 1: normal hepatic function, Group 2: mild hepatic impairment, and Group 3: moderate hepatic impairment). Data for all study subjects combined were presented, when appropriate.
Plasma concentrations were summarized using descriptive statistics for each study group. A subject listing of all plasma concentration-time data for each study group was presented.
Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of plasma concentrations for SU011248, SU012662 and total drug, were presented in tabular form by study group, study day, and nominal time. No correction was made for differences in molecular weights before summarization of SU011248+SU012662 concentration data, because the differences are negligible.
Linear and semi-log plots of median plasma concentrations by nominal time for SU011248, SU012662, and total plasma concentrations were prepared with data from all study groups in the same plot (separated only by analytes). Similar plots were prepared for the plasma concentrations of each individual patient.

RESULTS

Subject Disposition and Demography: Twenty-four subjects (16 men, 8 women; 21 white, 2 black, and 1 Asian; 48 to 78 years of age) were enrolled in and completed the study. As required by the protocol, 8 of the subjects had mild hepatic impairment, and 8 had moderate hepatic impairment.

Pharmacokinetic Results: Only pharmacokinetic measurements and analyses were performed for this study. Measurable SU011248 concentrations were achieved within 1 hour after dosing and remained quantifiable at all following time points until at least Day 15, in all subjects except Subject 10021030. Measurable SU012662 concentrations were achieved within 1 hour after dosing in most subjects and were quantifiable at all following time points until at least Day 17, in all subjects except Subject 10021030. Peak SU011248 and SU012662 concentrations were achieved at approximately 6 to 10 hours after dosing (median Tmax), followed by a bi-exponential decline.

The pharmacokinetics of SU011248 and SU012662 were variable in both normal and hepatic-impaired subjects in this study. In the case of SU011248, inter-subject coefficients of variation (CVs) on measures of total exposure (AUC_{inf}, AUC_{last}, and C_{max}) ranged from 12.8% to 40.3%, and on measures of unbound exposure ($AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$) ranged from 13.8% to 40.5 %. For SU012662, inter-subject CVs for total exposure (AUC_{inf}, AUC_{last}, and C_{max}) ranged from 25.4% to 54.2%, and on measures of unbound exposure ($AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$) it ranged from 25.9% to 52.6%.

Table S1: PK parameters for sunitinib, SU012662 and combined drug for normal, mild and moderate hepatic impairment groups.

Parameter	Geometric Mean (95% Confidence Interval)		
	Normal N=7	Mild N=8	Moderate N=8
SU011248 Total			
AUC_{inf} (ng·h/mL)	1368.7 (1242.7, 1507.5)	1514.2 (1369.2, 1674.6)	1477.2 (1431.0, 1524.8)
AUC_{last} (ng·h/mL)	1354.8 (1228.8, 1493.7)	1484.6 (1344.8, 1639.0)	1454.7 (1408.3, 1502.5)
C_{max} (ng/mL)	21.9 (19.9, 24.0)	23.3 (22.2, 24.4)	22.7 (21.4, 24.0)
T_{max} (h)[a]	8.1 (6.0, 16.0)	8.0 (4.0, 12.0)	10.0 (1.0, 16.0)
$t_{1/2}$ (h)	63.8 (61.7, 65.9)	79.5 (75.3, 83.9)	79.2 (73.9, 84.9)
CL/F (L/h)	36.5 (33.2, 40.2)	33.0 (29.9, 36.5)	33.8 (32.8, 34.9)
SU011248 Unbound			
Fu (%)	9.8 (9.6, 10.1)	8.0 (7.7, 8.4)	9.0 (8.8, 9.2)
$AUC_{inf,u}$ (ng·h/mL)	134.5 (124.3, 145.5)	121.3 (111.5, 131.9)	132.7 (128.2, 137.4)
$AUC_{last,u}$ (ng·h/mL)	133.1 (122.9, 144.2)	118.9 (109.6, 129.0)	130.7 (126.3, 135.2)
$C_{max,u}$ (ng/mL)	2.2 (2.0, 2.3)	1.9 (1.8, 2.0)	2.0 (1.9, 2.1)
SU012662 Total			
AUC_{inf} (ng·h/mL)	559.4 (517.8, 604.4)	491.9 (459.7, 526.3)	505.1 (461.4, 552.9)
AUC_{last} (ng·h/mL)	530.7 (489.8, 575.0)	456.4 (428.5, 486.1)	475.0 (432.0, 522.3)
C_{max} (ng/mL)	4.3 (4.0, 4.7)	4.3 (4.0, 4.7)	4.3 (3.7, 5.0)
T_{max} (h)[a]	6.1 (6.0, 12.0)	6.0 (4.0, 48.0)	6.0 (1.0, 36.0)
$t_{1/2}$ (h)	110.9 (107.1, 114.7)	121.9 (114.4, 129.8)	112.6 (107.4, 118.1)
SU012662 Unbound			
Fu (%)	16.0 (15.5, 16.6)	13.5 (13.0, 14.1)	15.6 (15.4, 15.7)
$AUC_{inf,u}$ (ng·h/mL)	89.7 (82.8, 97.2)	66.6 (62.6, 70.9)	78.6 (72.1, 85.7)
$AUC_{last,u}$ (ng·h/mL)	85.1 (78.4, 92.3)	61.8 (58.2, 65.6)	73.9 (67.5, 81.0)
$C_{max,u}$ (ng/mL)	0.7 (0.6, 0.8)	0.6 (0.5, 0.6)	0.7 (0.6, 0.8)
Total Drug*			
AUC_{inf} (ng·h/mL)	1937.8 (1784.4, 2104.4)	2001.9 (1828.4, 2191.9)	1999.1 (1940.5, 2059.4)
AUC_{last} (ng·h/mL)	1912.6 (1759.9, 2078.4)	1956.1 (1794.1, 2132.7)	1958.4 (1896.8, 2022.0)
C_{max} (ng/mL)	26.0 (23.8, 28.5)	27.3 (26.0, 28.7)	26.7 (25.0, 28.6)
T_{max} (h)[a]	6.1 (6.0, 12.0)	8.0 (4.0, 12.0)	8.0 (1.0, 16.0)

Pairwise comparisons demonstrated that systemic exposure (AUC_{inf}, AUC_{last} and C_{max}) of SU011248, SU012662, and Total Drug was not significantly changed in subjects with mild and moderate hepatic impairment, compared with normal subjects.
Median T_{max} for SU011248 was not significantly different in normal subjects (median T_{max} = 8.1 hours) compared with subjects with mild impairment (median T_{max} = 8.0 hours) and subjects with moderate impairment (median T_{max} = 10.0 hours). Median T_{max} for SU012662 was similar in all 3 study groups (6.0 hours – 6.1 hours), although the ranges were wide. Mean SU011248 $t_{1/2}$ was slightly longer in subjects with hepatic impairment (79.2 hours-79.5 hours) compared with normal subjects (63.8 hours).
Point estimates of the geometric LS mean ratio (mild/normal and moderate/normal) for SU011248t 1/2 fell within the 80% to 125% range; the 90% CI was 102% - 151%.
SU012662 t1/2 was similar across groups (112.6 hours – 121.9 hours in subjects with hepatic impairment and 110.9 hours in normal subjects). CL/F of SU011248 was not significantly different in subjects with hepatic impairment (33.0 L/h-33.8 L/h) compared with normal subjects (36.5 L/h).
The unbound fractions of SU011248 and SU012662 were slightly smaller in the hepatic impaired groups, compared with the normal group. For SU011248, the unbound fraction in the hepatic-impaired groups was 8.0% to 9.0 %, compared with 9.8% in the normal group. For SU012662, the unbound fraction in the hepatic-impaired groups was 13.5% to 15.6%, compared with 16.0% in the normal group. No significant differences between groups in protein binding can be concluded given the intrinsic variability of the protein-binding assay.
Pairwise comparisons of unbound PK parameters demonstrated that unbound exposure ($AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$) of SU011248 was not significantly changed in subjects with mild and moderate hepatic impairment, compared with normal subjects. SU012662 unbound PK parameters were similar in hepatic-impaired subjects compared with, apart from $AUC_{inf,u}$ and $AUC_{last,u}$, which appeared to be slightly lower in the mild impairment group.
Table S2: Geometric mean ratios for sunitinib, SU012662 and combined drug in mild/normal and moderate/normal groups.

Parameter	Geometric Least Squares Mean Ratio (90% Confidence Interval)	
	Mild/ Normal	Moderate/ Normal
SU011248 Total		
AUC_{inf} (ng·h/mL)	1.11 (0.84, 1.47)	1.08 (0.81, 1.43)
AUC_{last} (ng·h/mL)	1.10 (0.83, 1.45)	1.07 (0.81, 1.42)
C_{max} (ng/mL)	1.06 (0.85, 1.34)	1.04 (0.82, 1.30)
T_{max}[a] (h)	0.35 (0.73)	-0.23 (0.82)
$t_{1/2}$ (h)	1.25 (1.03, 1.51)	1.24 (1.02, 1.51)
CL/F (L/h)	0.90 (0.68, 1.20)	0.93 (0.70, 1.23)
SU011248 Unbound		
Fu (%)	0.82 (0.73, 0.92)	0.91 (0.81, 1.03)
$AUC_{inf,u}$ (ng·h/mL)	0.90 (0.71, 1.14)	0.99 (0.78, 1.25)
$AUC_{last,u}$ (ng·h/mL)	0.89 (0.71, 1.13)	0.98 (0.78, 1.24)
$C_{max,u}$ (ng/mL)	0.87 (0.71, 1.07)	0.95 (0.77, 1.17)
SU012662 Total		
AUC_{inf} (ng·h/mL)	0.88 (0.67, 1.16)	0.90 (0.69, 1.19)
AUC_{last} (ng·h/mL)	0.86 (0.65, 1.14)	0.90 (0.68, 1.18)
C_{max} (ng /mL)	1.00 (0.67, 1.48)	0.99 (0.66, 1.46)
T_{max}[a] (h)	2.16 (0.03)	0.70 (0.48)
$t_{1/2}$ (h)	1.10 (0.92, 1.31)	1.02 (0.85, 1.21)
SU012662 Unbound		
Fu (%)	0.84 (0.76, 0.94)	0.97 (0.87, 1.09)
$AUC_{inf,u}$ (ng·h/mL)	0.74 (0.57, 0.97)	0.88 (0.67, 1.14)
$AUC_{last,u}$ (ng·h/mL)	0.73 (0.55, 0.95)	0.87 (0.66, 1.14)
$C_{max,u}$ (ng/mL)	0.84 (0.56, 1.26)	0.96 (0.64, 1.43)
Total Drug (SU011248 + SU012662)		
AUC_{inf} (ng·h/mL)	1.03 (0.80, 1.33)	1.03 (0.80, 1.32)
AUC_{last} (ng·h/mL)	1.02 (0.80, 1.31)	1.02 (0.80, 1.31)
C_{max} (ng/mL)	1.05 (0.83, 1.33)	1.03 (0.81, 1.30)
T_{max}[a] (h)	-0.29 (0.77)	-0.52 (0.60)

Safety Results: During the course of the study, no subject died, no subject experienced an SAE, and no dose modifications or temporary or permanent discontinuations from study treatment were needed. All AEs were graded mild (Grade 1), moderate (Grade 2), or severe (Grade 3), based on the MedDRA (v. 9.0) dictionary.

The overall incidence of AEs was low. All subjects were evaluable for AEs. Six of the 8 subjects in Group A (normal hepatic function) reported a total of 16 AEs. Two of the 8 subjects in Group B (mild hepatic impairment) reported a total of 3 AEs. None of the 8 subjects in Group C (moderate hepatic impairment) reported an AE.

The AEs most frequently reported were gastrointestinal disorders (6 AEs), all reported by subjects in the normal group. Subjects in the normal group also accounted for all reported AEs in general disorders and administration site conditions (2 AEs); musculoskeletal and connective tissue disorders (2 AEs); respiratory, thoracic, and mediastinal disorders (1 AE); and skin and subcutaneous tissue disorders (3 AEs). Subjects in the mildly impaired group experienced the only occurrences of metabolism and nutrition disorders (1 AE) and psychiatric disorders (1 AE).

Subjects in the normal group and the mildly impaired group reported nervous system disorders (normal group - 2 AEs; mildly impaired group - 1 AE). One of these subjects (Subject 10021030) had an AE of emesis soon after dosing. Available data for this subject were included in individual listings of SU011248, SU012662, Total Drug concentrations, and PK parameters, but were excluded from summary statistics.

CONCLUSIONS

- Mean SU011248 AUC_{inf}, AUC_{last}, and C_{max} were similar between subjects with hepatic impairment and normal subjects.
- Mean SU012662 AUC_{inf}, AUC_{last}, and C_{max} were similar between subjects with hepatic impairment and normal subjects.
- SU011248 was safe and well tolerated by the subjects participating in the study. No subject experienced an SAE, and no subject discontinued the study because of an AE.
- Dose adjustment of SU01248 is not necessary for patients with mild to moderate hepatic impairment.

5. PHARMACOMETRICS REVIEW

Summary:

The sponsor conducted an exposure-response analysis to evaluate the relationship between combined sunitinib+SU012662 exposure and measures of effectiveness in treatment-naïve and cytokine-refractory patients with metastatic renal cell carcinoma (MRCC). Time to tumor progression, response rates and changes in tumor size were modeled as a function of sunitinib exposure.
There was no effect of AUC on time to tumor progression or death, probably due to the small number of patients with observed tumor progression or death in the first-line treatment-naïve patients. However, there was a significant correlation of AUC of sunitinib with the probability of a partial response in cytokine refractory patients, suggesting a 1.9-fold increase in the probability of a PR with each unit increase in AUC.

The tumor growth dynamics model provided a good description of changes in tumor size with sunitinib treatment. Line of therapy (treatment-naïve or cytokine refractory), baseline tumor size, sex and ECOG score were not significantly associated with changes in tumor size with sunitinib treatment. Using the model and assuming perfect patient compliance, simulation of tumor growth dynamics for the 50 mg QD (4/2 schedule) showed that 62% of patients would be classified as partial responders by RECIST criteria (i.e., 30% reduction in tumor volume).

The applicant's analysis is acceptable. There are no recommendations at this time.

Data:

The studies included in the data analysis included the phase 3 study of sunitinib vs. IFN-a from the current submission (study A6181034) as well as two phase 2 studies of sunitinib (single-arm studies RTKS-0511-014 and A6181006) submitted at the time of the original NDA review. Table PM1 provides a summary of the three studies included in the analysis.

Table PM1: Sunitinib studies included in the exposure-response analysis. All studies used the L-malate salt capsule formulation

Protocol	Design	Treatment Duration	# Patients With Evaluable PK	Doses	PK Sampling	PD Evaluation
RTKC-0511-014 (Study 014)	open-label, single-arm, multicenter, clinical trial evaluating the efficacy and safety as single-agent, second-line therapy in MRCC patients	6 week cycles on Schedule 4/2	56	50 mg QD with dose reduction if needed. Dose range: 25-62.5 mg QD	Trough sampling at Days 14 and 28 of Cycle 1, Day 28 of each additional cycle	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies, and clinical assessments at Days 14 and 28 of Cycle 1, Day 28 of each additional cycle

A6181006 (Study 1006)	open-label, single-arm, multicenter, trial evaluating the efficacy and safety as a single-agent in MRCC patients	6 week cycles on Schedule 4/2	92	50 mg QD. Dose range: 25-62.5 mg QD	Trough sampling at Days 14 and 28 of Cycle 1, Day 28 of each additional cycle	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies and clinical assessments at Days 14 and 28 of Cycle 1, Day 28 of each additional cycle
A6181034 (Study 1034)	Randomized study of sunitinib versus Interferon-α as first-line systemic therapy for patients with MRCC	6 week cycles on Schedule 4/2	44	50 mg QD with dose reduction if needed. Dose range: 25-50 mg QD	Trough sampling at Days 14 and 28 of Cycle 1, Day 28 of each additional cycle	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies and clinical assessments at Days 14 and 28 of Cycle 1, Day 28 of each additional cycle

Exposure measures:

Population PK models for the parent and metabolite were used to obtain estimates of exposures for each patient in the three studies. Population PK models for the parent and metabolite were used, as only trough levels were available for a majority of the patients in the dataset. The PK of sunitinib was described using a 2-compartment model with the parameters for oral clearance (CL/F) of central and peripheral compartments, volume of distribution of central and peripheral compartments, and first-order rate of absorption. The SU012662 (sunitinib primary metabolite) PK were described similarly with a 2-compartment model. The fraction of sunitinib metabolized to SU012662 was assumed to be 21% based on preclinical data.2 Bioavailability of both parent and metabolite after oral administration could not be assessed, as no intravenous formulation was available. Full population PK models were developed separately for sunitinib and SU012662 utilizing all available relevant PK study data as part of the original NDA submission.

Area under the curve at steady-state (AUC) for sunitinib and SU012662 was calculated from the average dose and estimated CL/F. Average dose was calculated from the patients dosing regimen history using all non-zero doses. Total drug AUC (AUCT) was calculated from the sum of average dose/CL/Fsunitinib + average dose*0.21/ CL/FSU012662 to account for conversion fraction of sunitinib to SU012662. Both measures were evaluated since both parent and metabolite have similar inhibitory profiles against target receptors. Molecular weight and plasma protein binding are similar between the 2 compounds, and thus the algebraic total was used.

Response measures:

Efficacy endpoints were based on the tumor volumes and Response Evaluation Criteria in Solid Tumors (RECIST). Repeated radiographic assessment at 6- to 12-week intervals using computerized tomography (CT) or magnetic resonance imaging (MRI) scans was performed for all tumor volume measurements. The RECIST defined responses are complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Confirmed responses

are those that persist on repeat imaging study at least 4 weeks after initial documentation of response.
The following endpoints were available at multiple time points for most patients in all studies:
• Tumor Volumes
• Investigator RECIST defined response, defined as the best confirmed individual RECIST response as reported by the study investigators.

The following endpoints were available at one time point for most patients:
• Investigator best overall confirmed RECIST defined response.
• Investigator time to tumor progression or Overall Survival (TTP/OS or TTPD), defined as the time from randomization to first documentation of objective tumor progression or to death due to cancer during the study, based on that patient's RECIST rating reported by the investigator.
• Duration of response was also assessed, although the data were not mature for analysis.

Three response measures were examined for exposure-response relationships:
1) Time to tumor progression or death (TTPD)
2) Overall response rate (ORR)
3) Change in tumor volumes

Software:

SAS version 9 was used for the non-parametric Kaplan-Meier analysis of effectiveness measures, as well as for the logistic regression analyses for response rates and toxicity measures. NONMEM (version V) was used for non-linear mixed-effects modeling of the parametric survival functions, as well as for the continuous variables among the toxicity measures.

Analysis:

The exposure-response analysis of Sutent in MRCC was necessarily limited to subjects with available PK data. Subjects without PK observations or those with incomplete or missing dosing data were excluded from the analysis. All patients from Study 1034 in which PK observations were taken were included in the analysis. The demographics of the subjects included in the analysis are described in Table PM2.

Table PM2: Subject demographics, by study.

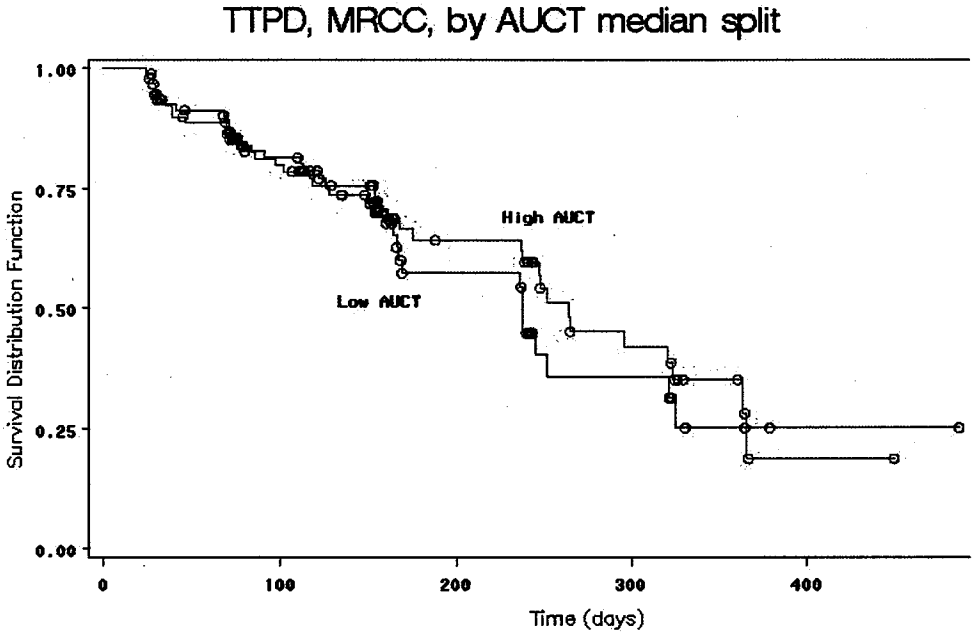
Covariate	Subgroup	Study 1006	Study 14	Study 1034	All
Number of Subjects		92	56	44	192
Line of Therapy	Treatment-Naïve (1st Line)	0	0	44	44
	Cytokine Refractory (2nd Line)	92	56	0	148
Gender	Males	60	37	29	126
	Females	32	19	15	66
Race	White	87	48	43	178
	Black	0	3	0	3
	Asian/Pacific Islander	1	3	1	5
	Other/Not Listed/Not Allowed	4	2	0	6
Average Weight (kg)		88	88	88	
Average Age (years)		56	59	62	

Two patients in Study 1034 and 4 patients in Study 14 with a left-censored TTP were removed from the TTP and lesion size analyses.

1) <u>Time to tumor progression or death (TTPD):</u>

To investigate the relationship between exposure to sunitinib or combined drug and TTPD, a Kaplan-Meier analysis was performed. The AUCtotal (combined AUC of sunitinib+SU012662) was split at the median (1.956 ng.hr/ml), and Kaplan-Meier curves, stratified based on AUCtotal less than or greater than the median, were plotted across all patients (Figure PM1). The plot shows a slight trend for a longer TTPD with an increase in AUCT.

Figure PM1: Kaplan-Meier curves for TTPD with combined AUC (AUCT) below the median (low AUC) and above the median (high AUC), across all patients.



A Weibull time-to-event model was fit to the TTPD data. The survival function was:

$$S(t)=\exp(-\text{lambda}\cdot t)^{\text{gamma}}$$

Lambda is the "rate constant" of the Weibull function and was modeled as a function of exposure (AUC).

$$\text{lambda} = \ln 2/(Eo+\text{Slope}\cdot AUC)$$

where Eo is the baseline (TTPD under untreated conditions), and Slope is the slope of the lambda-AUC relationship.
Both linear and Emax models were used to model the effect of exposure, and compared to the base model where Slope was set to zero.

The following table shows the summary of the model fitting.

Table PM3: Results of parametric survival model fitting to data across all MRCC studies.

No.	Model	OBJ	B1	gamma	Slope	Emax	EC50	ETA
1	Base	1010.214	263	2.1	0 (fixed)	-	-	84.5%
2	Linear	1009.344	182	2.1	40.7	-	-	83.5%
3	Emax	1009.380	170	2.1	-	645	11.8	83.5%

Results showed that no relationship could be established between TTPD and exposure. Inclusion of AUCT in the model did not result in a significant decrease in the objective function compared to the base model. The data was severely limited by the absence of an untreated or placebo group.

2) <u>Overall Response Rate (ORR):</u>
The following table shows the confirmed objective response rates by study for the three studies included in the dataset.

Table PM3: Best confirmed objective response rates for MRCC studies, by treatment in dataset.

Response [n (%)]	Study 1006	Study 14	Study 1034
	N=92	N=54	N=42
Complete Response (CR)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Partial Response (PR)	35 (38.0%)	23 (42.6%)	13 (30.1%)
Stable Disease (SD)	38 (41.3%)	22 (40.7%)	21 (50.0%)
Disease Progression (PD)	14 (15.2%)	6 (11.1%)	1 (2.4%)
Not evaluable/Missing	4 (4.4%)	3 (5.6%)	7 (16.7%)

Since the major response seen was the partial response (PR), the proportion of PR patients was evaluated as a function of exposure using logistic regression, to examine E-R relationships for sunitinib in MRCC patients. The analysis was limited to patients with confirmed RECIST scores. Analysis was done on the complete dataset as well as for first-line (treatment-naïve) patients and second-line (cytokine-refractory) patients separately.
The following table shows the summary of the results. When the complete dataset was analyzed, the relationship between probability of partial responses and AUCT did not reach statistical

significance (p=0.07). When the data for first-line patients was analyzed separately, there was no relationship between probability of partial responses and AUCT. This was probably due to the limited sample size (sample size was limited only to the patients who had PK data).
The data for second-line patients showed a significant relationship between probability of partial responses and AUCT. The resulting odds ratio suggested a 1.9-fold increase in the frequency of partial responses for each unit increase in AUC of combined drug (sunitinib+SU012662). The However, this model is also somewhat limited by the lack of placebo data to define the true baseline (untreated) probability in this population.

Table PM4: Results of logistic regression analysis of partial responses vs. AUC of combined (sunitinib+SU012662) drug.

Dataset	Independent variables	Estimate	SE	p-value	Odds Ratio
ALL DATA (study 14, 1006, 1034)	Intercept AUCT	-1.38 0.50	0.59 0.28	0.0185 0.0727	**1.65 (0.96 – 2.86)**
FIRST-LINE (study 1034)	Intercept AUCT	-0.10 -0.23	1.42 0.74	0.9463 0.7546	-
SECOND-LINE (study 14, 1006)	Intercept AUCT	-1.60 0.62	0.66 0.31	0.0149 0.0445	**1.86 (1.02 – 3.40)**

Figures PM2-PM4 show the probability of partial responses vs. AUCT, plotted for all data, and separately for first- and second-line patients.

Based on the above estimates, the probability of partial responses (PR) can be predicted at various AUCs. The predicted frequency of PR for the lowest quartile of AUC (mean AUC in lowest quartile: 1.34 ng.h/ml) was 0.29, and for the highest quartile of AUC (mean AUC in highest quartile: 2.78 ng.hr/ml) was 0.57. The predicted frequency of PR for the median AUC (1.99 ng.hr/ml) was 0.41.

Figure PM2: Probability of partial responses vs. AUC total (sunitinib+SU012662) for all patients (first- and second-line patients).

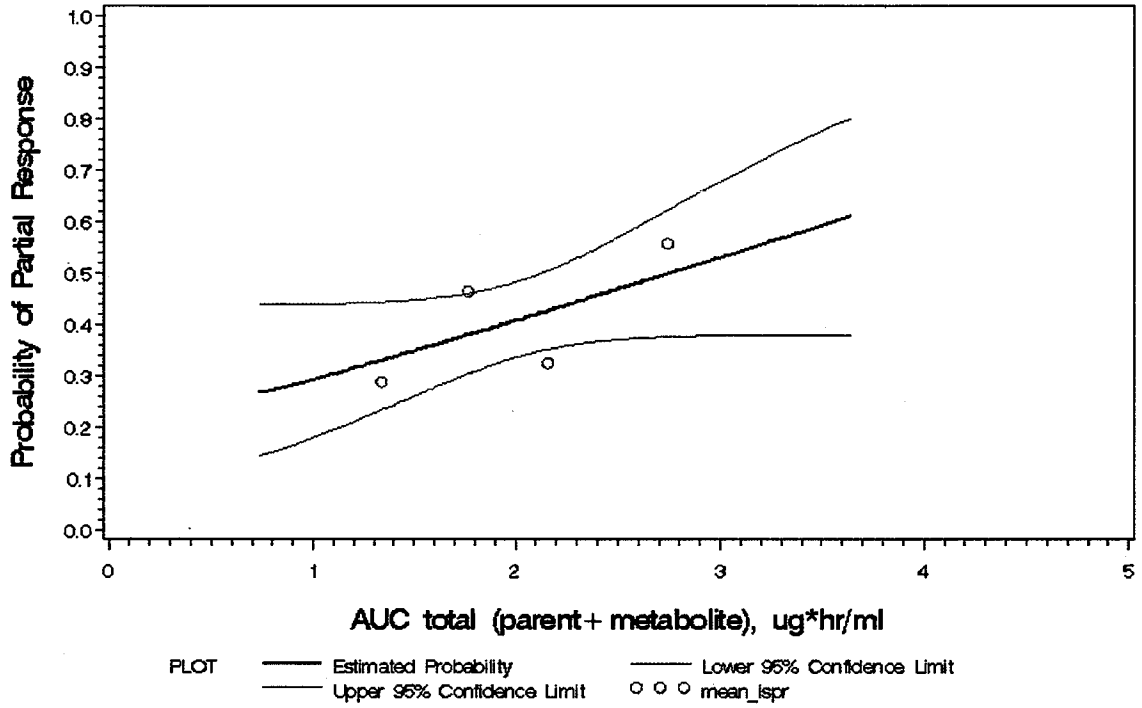


Figure PM3: Probability of partial responses vs. AUC total (sunitinib+SU012662) for first-line (treatment-naïve) patients.

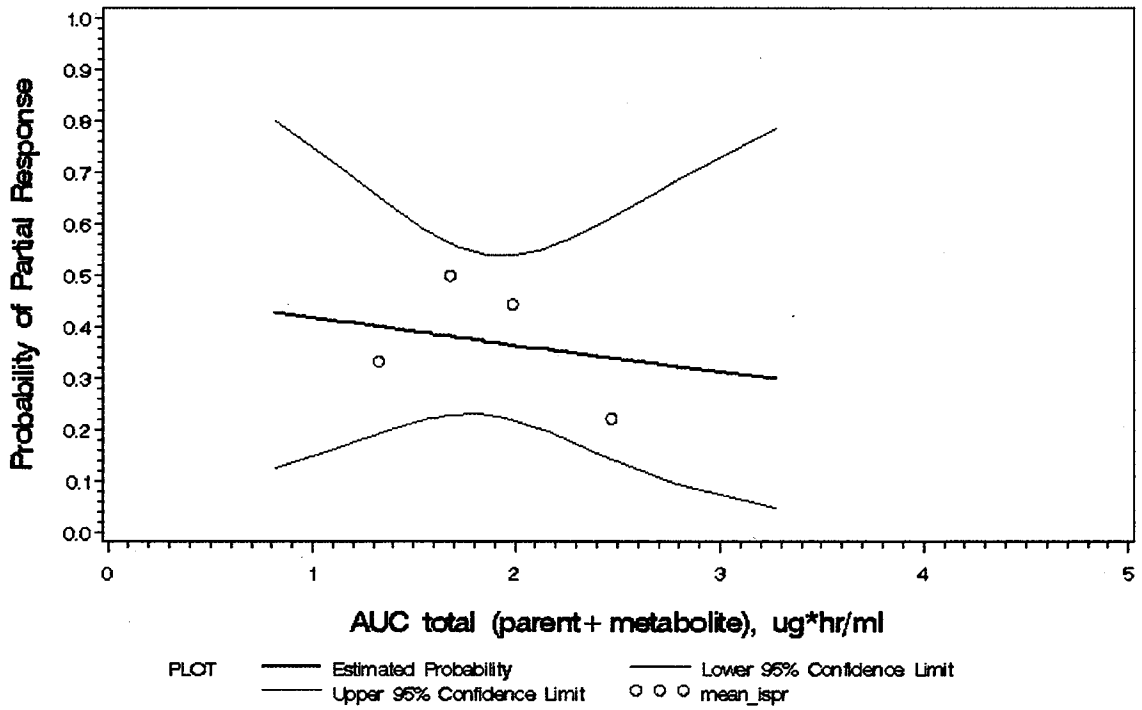
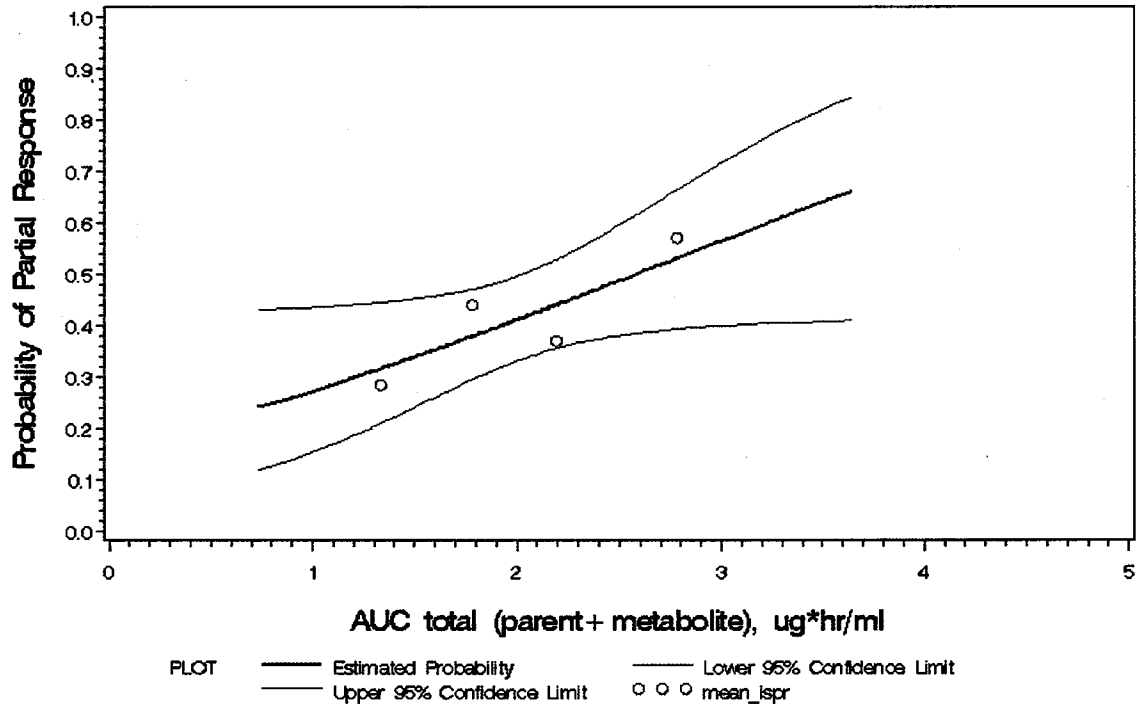


Figure PM4: Probability of partial responses vs. AUC total (sunitinib+SU012662) for second-line (cytokine-refractory) patients.

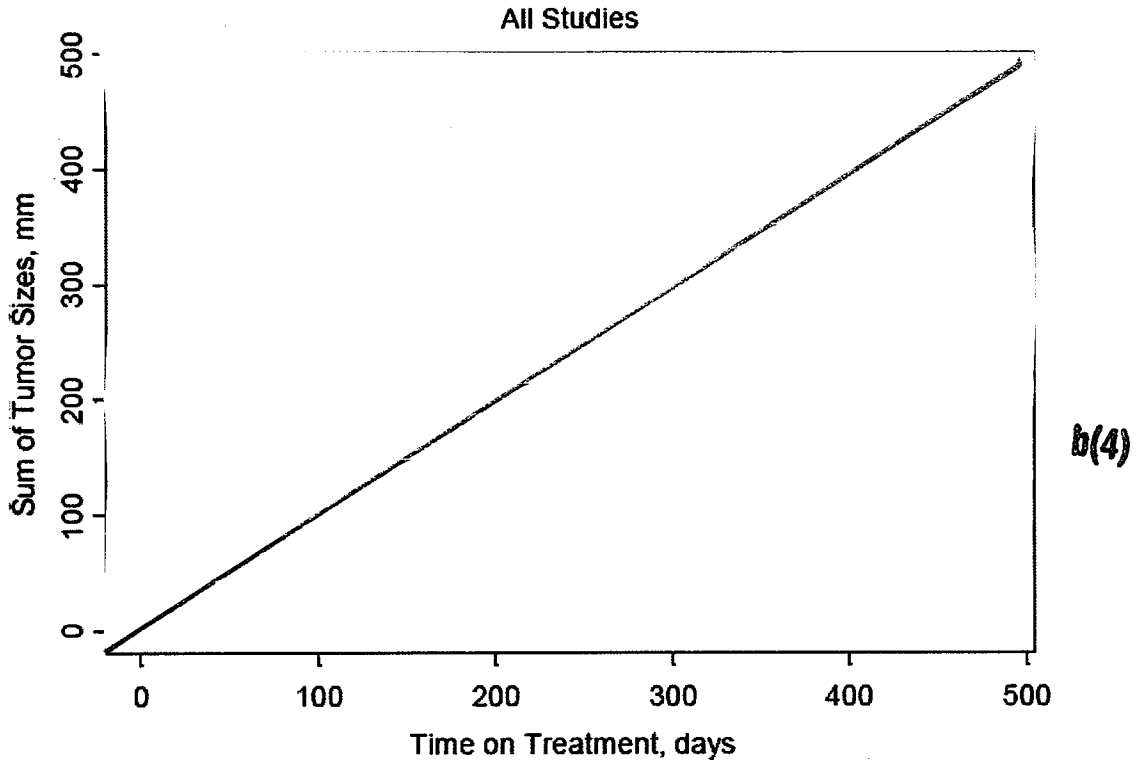


3) Tumor growth dynamics modeling:

To examine the effect of sunitinib and total drug on changes in tumor volumes, the sponsor developed a parametric exposure-response model relating tumor size (sum of lesion lengths) to exposure measures following multiple doses of sunitinib in patients with MRCC. This model was further used to identify factors that affect the exposure versus tumor response relationship. The measure of exposure used was the AUC for sunitinib. Covariates evaluated for their impact on tumor dynamics were: (1) sex, (2) line of treatment (treatment-naïve versus cytokine refractory), (3) race, and (4) baseline tumor size.

Tumor sizes collected at timed intervals in patients with MRCC are shown in figure PM5. The analyzed data set included only that subset of patients for whom PK data was collected and exposure measurements could be determined.

Figure PM5: Time course of observed tumor sizes in MRCC patients. The sponsor included median curves for patients with PK data and patients without PK data. Only patients with PK data were included in the tumor growth dynamics model.



A tumor growth dynamics model was developed to describe the relationship between tumor size and AUC, as follows:

$$\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D \cdot AUC \cdot R(t) \cdot y(t)$$

where y(t) is the sum of lesion lengths at time t (at time 0, y(0) = y0)
K_L is tumor growth rate (day-1)
K_D **is tumor kill rate (ng•h•ml-1 • day-1)**
AUC is the measure of drug exposure (ng•h•ml-1)
R(t) describes resistance of the tumor to the drug with a rate constant of resistance, λ (day-1) by the relationship R(t) = e-λ t.

Inter-subject variability on the tumor growth model parameters (K_D and λ) was modeled using exponential error terms. Residual variability was modeled as an additive error.
The effect of several covariates on K_D and λ were evaluated. The sponsor developed a full model with all covariates in the model and performed a stepwise backward elimination process to eliminate those covariates whose exclusion did not impact on the fit (as determined by change in OFV significant at the $p<0.01$ level).

Goodness of fit was evaluated by successful minimization, successful covariance estimation, change in objective function, visual inspection of scatter-plots (observed vs. predicted as well as residual plots), and precision of the parameter estimates.

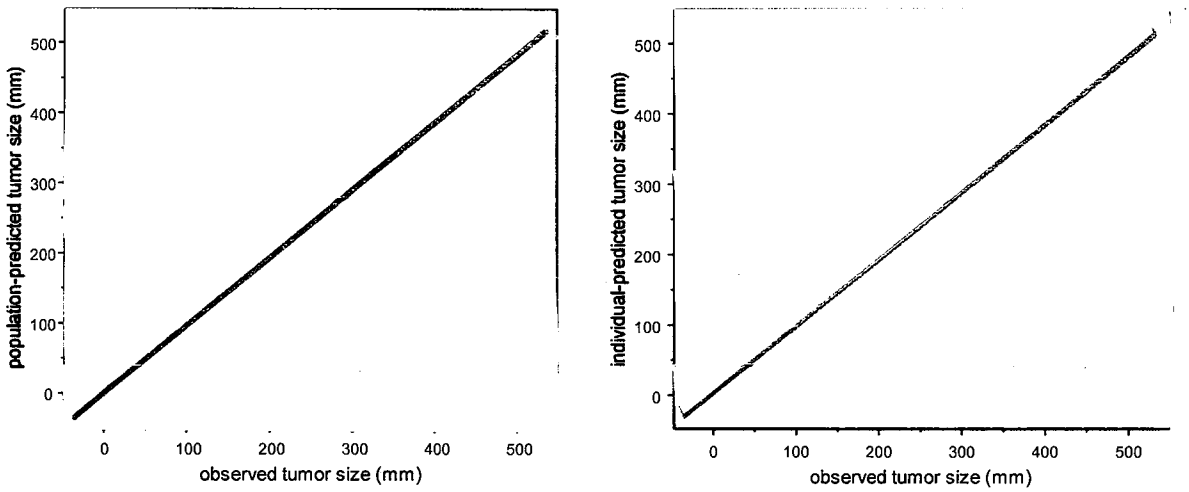
The Agency's analysis essentially replicated the modeling done by the sponsor with the exception that the ECOG score was included as a covariate in the analysis, and race was not included in the analysis as only 14 of the 188 patients (less than 10%) belong to a race other than White.

The base model was adequately fit to the data. Figure PM6 shows the diagnostic plots for the base model. The appendix shows the residual plots of the inter-individual variability in K_D and λ vs. potential covariates.

Analysis of covariates showed a marginally significant effect of SEX on K_D (table PM5). The change in OFV was just above the threshold for significance at the 0.01 level. The inclusion of SEX in the model did not impact on the inter-individual variability of KD, further suggesting that this was not a major effect. No further effects of any other covariates were noted. These results **are somewhat consistent with the sponsor's analysis**, which also showed an initial effect of SEX on K_D, during covariate selection, however the effect was not retained during further backward elimination steps.

The model parameters for the final model are listed in table PM6.

Figure PM6: Diagnostic plots for base model of tumor growth dynamics model. Left: population-predicted vs. observed, Right: individual-predicted vs. observed.



b(4)

Table PM5: Steps in model fitting of tumor growth dynamics model to MRCC data.

Model	Description	OFV	Delta OFV	KL	KD	λ	ETASD KD	ETASD λ
1	Base	4187.399	-	0.00303	0.00558	0.00652	65%	77%
2	#1 + SEX on KD	4180.737	6.66 p<0.01	0.00306	0.00619	0.00651	63%	77%
3	#2 + LINE on KD	4177.718	3.01 NS	0.0031	0.00741	0.00645	62%	76%
4	#2 + Baseline on KD	4179.530	1.21 NS	0.00305	0.00624	0.00663	63%	76%
5	#2 + ECOG on KD	4180.737	0.0 NS	0.00306	1.09	0.00651	63%	77%
6	#2 + SEX on λ	4177.129	3.608 NS	0.00305	0.00634	0.0074	63%	74%
7	#2 + LINE on λ	4180.746	-0.009 NS	0.00307	0.00617	0.00257	63%	77%
8	#2 + Baseline on λ	4175.326	5.411 NS	0.00312	0.00604	0.00564	63%	75%
9	#2 + ECOG on λ	4180.737	0 NS	0.00306	0.00619	0.0273	63%	77%

Table PM6: Model parameters for the final model of tumor growth dynamics.

Parameter	Estimate (SE)	%Inter-individual variability (Relative SE)
KL (day-1)	0.00308 (0.00122)	
KD (ng.hr.ml-1.day-1)	0.00558 (0.00076)	65% (29%)
λ (day-1)	0.00652 (0.00235)	77% (37%)
Residual Error (mm)	11 (4.8)	

Prediction of tumor volume changes: Simulations were performed to predict the effect of various doses of sunitinib on tumor growth dynamics. The doses evaluated were 25, 37.5, 50, and 75 mg QD on a 4/2 schedule. The average AUC predicted from the population PK model for each dose was used to predict tumor volume changes as a function of time at the mean exposure level for each dose. Figure PM7 shows the results of the simulations and table PM7 lists the estimated proportion of patients meeting RECIST criteria for a partial response (i.e., ≥30% maximum reduction from baseline in tumor volume at any time-point in the study). The model suggests that with perfect compliance and drug tolerance, 62% of patients would be expected to be classified as partial responders at the dose of 50 mg QD on a 4/2 schedule (table PM8). Furthermore, the model suggests that decreasing the dose to 37.5 mg QD on a 4/2 schedule would be associated with a 20% lower response rate (i.e., 41% of patients with ≥30% maximum reduction from baseline in tumor volume at any time-point in the study). However, this model should be interpreted with caution, as it is not able to extrapolate to other dosing schedules (i.e., schedules other than 4/2).

Figure PM7: Simulations showing the predicted population mean effect of different doses on the 4/2 schedule on tumor growth dynamics for sunitinib.

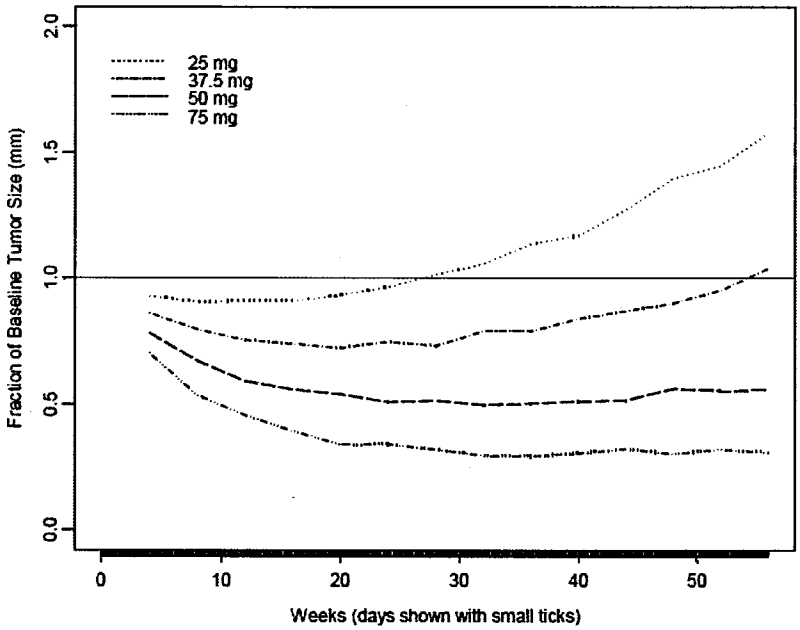


Table PM7: Percent of patients who achieve >30% decrease in tumor size from baseline at different sunitinib doses.

Sutent Dose (mg) on a 4/2 Schedule	% of Patients Achieving ≥30% Decrease From Baseline Tumor Size
25	23.0
37.5	41.3
50	61.8
75	68.5

Conclusions:

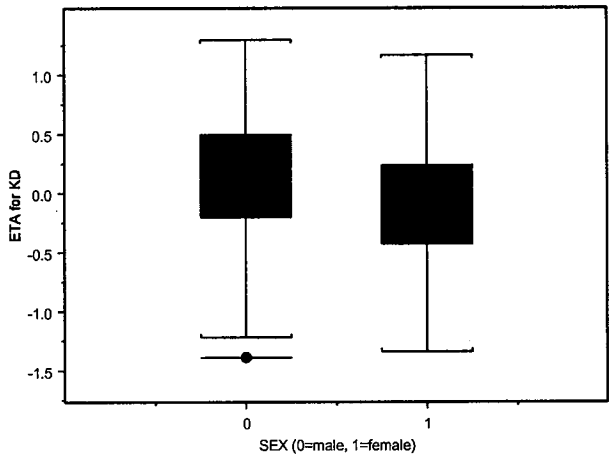
The objective of this analysis was to explore the exposure-response relationship between sunitinib and total drug and selected efficacy measures in treatment naïve and cytokine refractory MRCC patients. The efficacy analysis focused on probability of observing a PR, TTP, DR, OS, and changes in tumor volumes. There was very little observed tumor progression or death for patients on sunitinib (5 uncensored observations of TTP and 1 uncensored observation of OS), limiting the ability to analyze exposure-response in treatment-naïve patients. However, there was a significant correlation of AUC of sunitinib with the probability of a partial response in cytokine refractory patients, suggesting a 1.6- to 2.9-fold increase in the probability of a PR with each unit increase in AUC. This was further supported by longer TTP, DR, and OS in cytokine refractory patients with high AUCs.

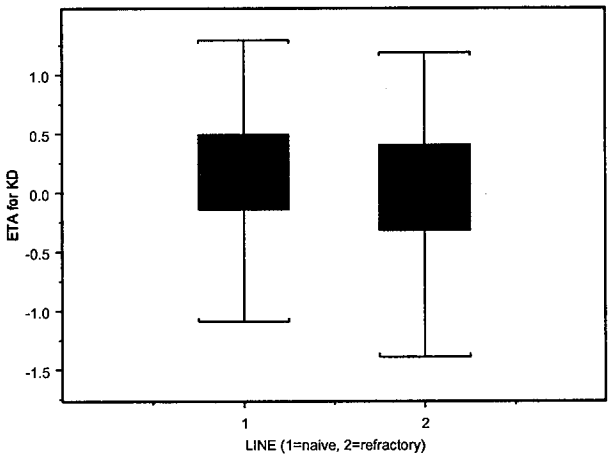
The tumor growth dynamics model provided a good description of changes in tumor size with sunitinib treatment. Line of therapy (treatment-naïve or cytokine refractory), baseline tumor size, sex and ECOG score were not significantly associated with changes in tumor size with sunitinib treatment. Using the model and assuming perfect patient compliance, simulation of the 50 mg

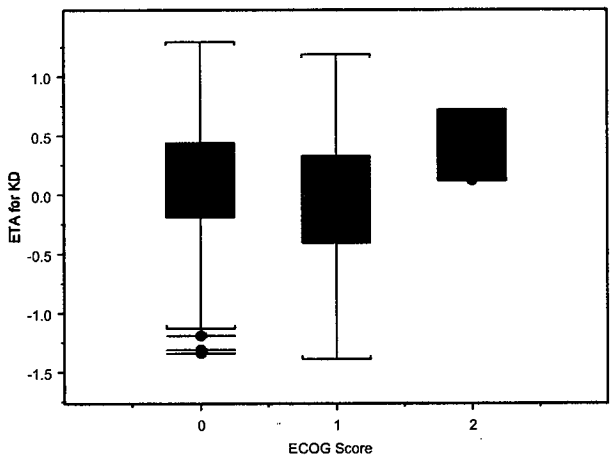
QD (4/2 schedule) showed that 62% of patients would be classified as partial responders by the RECIST criteria (i.e., 30% reduction in tumor volume).

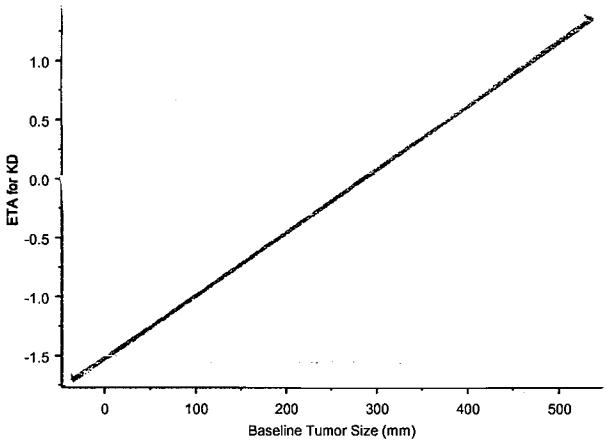
APPENDIX TO PM REVIEW

Inter-individual variability in KD from base model plotted vs. potential covariates sex, line of treatment, baseline tumor size and ECOG score.



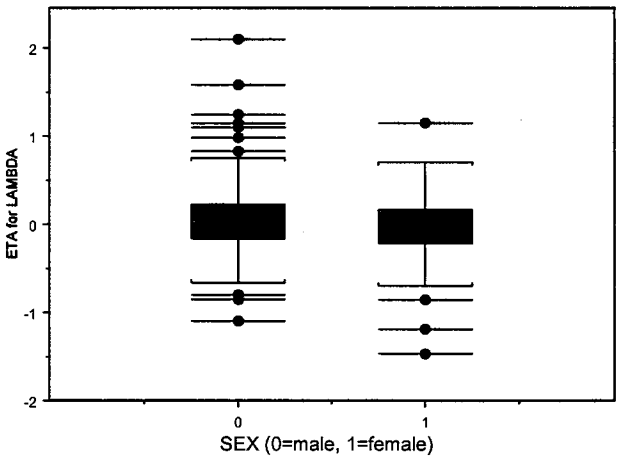


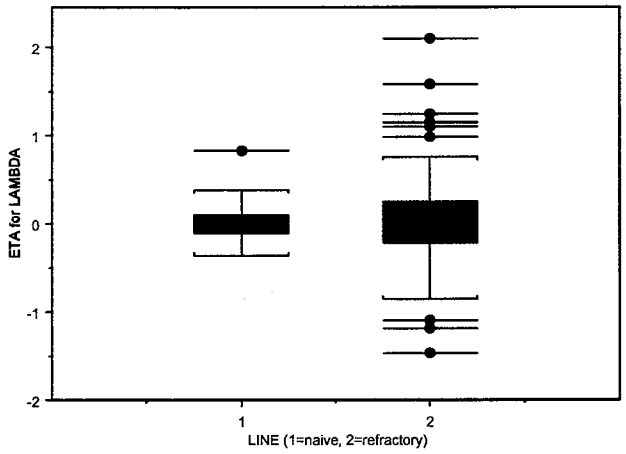


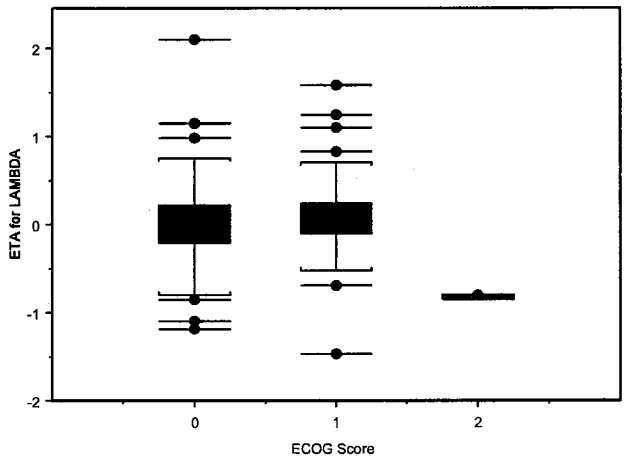


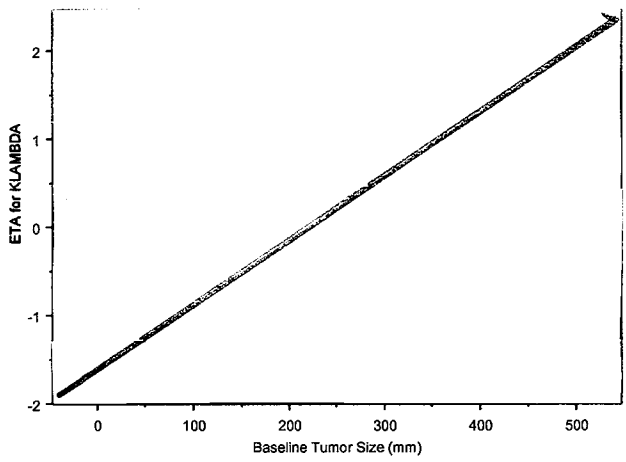
b(4)

Inter-individual variability in λ from base model plotted vs. potential covariates sex, line of treatment, baseline tumor size and ECOG score.




ETA for LAMBDA
2
1
0
-1
-2
1
2
LINE (1=naive, 2=refractory)


ETA for LAMBDA
2
1
0
-1
-2
0
1
2
ECOG Score


ETA for KLAMBDA
2
1
0
-1
-2
0
100
200
300
400
500
Baseline Tumor Size (mm)

b(4)

6. OCPB Filing and Review Form

Office of Clinical Pharmacology **New Drug Application Filing and Review Form**			
General Information About the Submission			
	Information		Information
NDA Number	21-938/21-968	**Brand Name**	SUTENT
OCP Division (I, II, III)	DCB-5	**Generic Name**	Sunitinib (SU-011248 L-Malate)
Medical Division	HFD-150	**Drug Class**	Anti-cancer
OCP Reviewer	Roshni Ramchandani	**Indication(s)**	(1) Treatment of gastrointestinal stromal tumors after failure of imatinib (2) Treatment of metastatic renal cell carcinoma [redacted]
OCP Team Leader	Brian Booth	**Dosage Form**	Capsules (12.5 mg, 25 mg, 50 mg)
		Dosing Regimen	50-mg once-daily, on a schedule of 4 weeks on treatment followed by 2 weeks off
Date of Submission	8/9/06	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	1/19/07	**Sponsor**	Pfizer Inc.
PDUFA Due Date	2/11/07	**Priority Classification**	P
Division Due Date	2/1/07		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter studies				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
Pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		Effect of hepatic impairment on sunitinib PK (study A6181079)

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		Phase 3 study comparing sunitinib and interferon-α in MRCC patients (Study A6181034). Exposure-Response analyses to be submitted 2 months after submission, per sponsor's cover letter.
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	2		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?	**X**	Please submit the results of your exposure-response analysis, both for measures of effectiveness and toxicity, for sunitinib in RCC patients, as indicated in your cover letter dated 8/9/06. Comments have been sent to firm (or attachment included).
QBR questions (key issues to be considered)	Effect of hepatic impairment on sunitinib pharmacokinetics. Extend PK model for sunitinib by including sparse data (trough levels) in phase 3 study. Exposure-response relationships for sunitinib for measures of effectiveness and toxicity in RCC patients.	
Other comments or information not included above		
Primary reviewer Signature and Date	Roshni Ramchandani	
Secondary reviewer Signature and Date	Brian Booth	

CC: NDA 21-938, HFD-850 (Electronic Entry), HFD-150 (Cottrell),
HFD-860 (Rahman, Booth, Gobburu, Ramchandani), CDR (Biopharm).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Roshni Ramchandani
1/29/2007 10:45:37 AM
BIOPHARMACEUTICS

Jogarao Gobburu
1/29/2007 10:50:20 AM
BIOPHARMACEUTICS

Brian Booth
1/29/2007 11:06:32 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

OTHER REVIEW(S)

DIVISION OF DRUG ONCOLOGY PRODUCTS
CSO LABELING REVIEW

NDA NUMBER: NDA 21-938 FA
NDA 21-938/SLR-002
NDA 21-938/SE8-003
NDA 21-938/SE8-004/005

NDA 21-968 FA
NDA 21-968/SLR-002
NDA 21-968/SE8-003/004/006
NDA 21-968/SE7-005

DRUG: SUTENT® (sunitinib malate) Capsules

SPONSOR: CP Pharmaceuticals International, CV

DATES OF SUBMISSIONS:

Submission	Receipt Date
NDA 21-938 FA	
NDA 21-938/SLR-002	March 30, 2006
NDA 21-938/SLR-002 BL	October 2, 2006
NDA 21-938/SE8-003	August 1, 2006
NDA 21-938/SE8-003 BL	October 2,2006
NDA 21-938/SE8-004	August 9, 2006
NDA 21-938/SE8-004 BL	September 29, 2006
NDA 21-938/SE8-004 BL	November 17, 2006
NDA 21-938/SE8-005	August 9, 2006
NDA 21-968 FA	
NDA 21-968/SLR-002	March 30, 2006
NDA 21-968/SLR-002 BL	October 2, 2006
NDA 21-968/SE8-003	March 31, 2006
NDA 21-968/SE8-003 BL	August 1, 2006
NDA 21-968/SE8-003 BL	October 2, 2006
NDA 21-968/SE8-004	March 31, 2006
NDA 21-968/SE8-004 BL	October 2, 2006
NDA 21-968/SE7-005	August 9, 2006
NDA 21-968/SE7-005 BL	November 17, 2006
NDA 21-968/SE7-005 BZ	September 29, 2006
NDA 21-968/SE8-006	August 9, 2006

BACKGROUND:

NDA 21-938 FA and NDA 21-968 FA provide for final printed labeling (FPL) submitted in response to the January 26, 2006, approval letter. This FPL has been superseded by the PLR labeling submitted with the efficacy supplements described below.

NDA 21-938/SLR-002 and NDA 21-968/SLR-002 provide for revisions to the labeling based on data from the following QT study: *"A Phase 1 Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors"*. This data was submitted in fulfillment of PMC # 7 from the January 26, 2006, approval letter.

NDA 21-938/SE8-003 and NDA 21-968/SE8-003 and 004 provide the study report of the first interim efficacy and safety analysis for the following study: *"A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma"*. The supplements also provide the datasets containing the core imaging facility assessments used to derive the updated response rate for the following study: *"A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma"*. Labeling revisions are proposed. These supplements are submitted in fulfillment of PMC #1 and #3 from the January 26, 2006, approval letter.

NDA 21-938/SE8-004 and NDA 21-968/SE7-005 provide the final study report and datasets from the following study: *"A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma"*. The supplements also provide follow-up left ventricular ejection fraction (LVEF) data for patients on the following study: *"A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma"*. The supplements propose labeling revisions based on the data provided. These supplements are submitted in fulfillment of PMC #2 and #4 from the January 26, 2006, approval letter.

NDA 21-938/SE8-005 and NDA 21-968/SE8-006 provide the final study report for the following study: *"A Phase I Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function"*. Labeling revisions are proposed based on the data submitted. This supplement is submitted in fulfillment of PMC #8 from the January 26, 2006, approval letter.

The sponsor confirmed that the labeling submitted with NDA 21-938/SE8-004 and 005 and NDA 21-968/SE7-005 and SE8-006 is a comprehensive label that incorporates all pending proposed changes (including those from NDA 21-938/SLR-002 and SE8-003 and NDA 21-968/SLR-002 and SE8-003 and 004). These supplemental applications also convert the labeling into the new Physician's Labeling Rule (PLR) format.

DISCUSSION:

Since the changes to convert the labeling into PLR format are extensive, individual PLR-conversion changes will not be outlined in this review. However, the following specific changes are proposed with these efficacy supplements:

1. In the **INDICATIONS AND USAGE** section, the indication has been changed as follows:

   "SUTENT is indicated for the treatment of advanced renal cell carcinoma. [redacted] b(4)

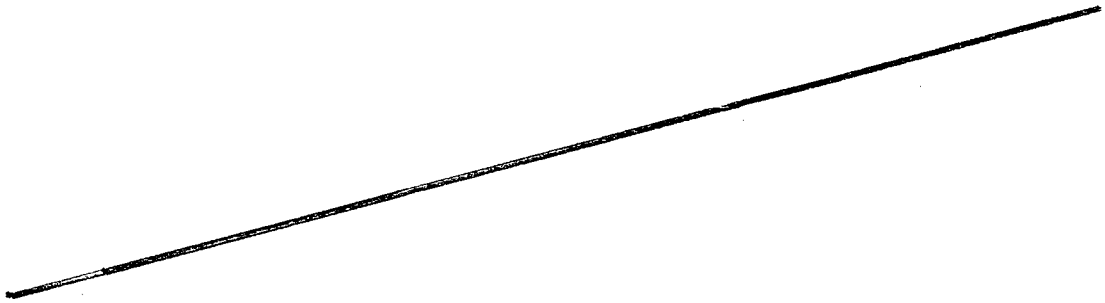
   has been changed to

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

   CSO Comment: This change has been reviewed by the team and is acceptable.

2. In the **WARNINGS AND PRECAUTIONS** section, **Left Ventricular Dysfunction** subsection, the following changes have been made to the first paragraph (additions shown as underlined text):

[redacted] b(4)



b(4)

CSO Comment: This change was reviewed by the team and revised wording was recommended to the sponsor during labeling negotiations. The final agreed-upon language for this section is as follows:

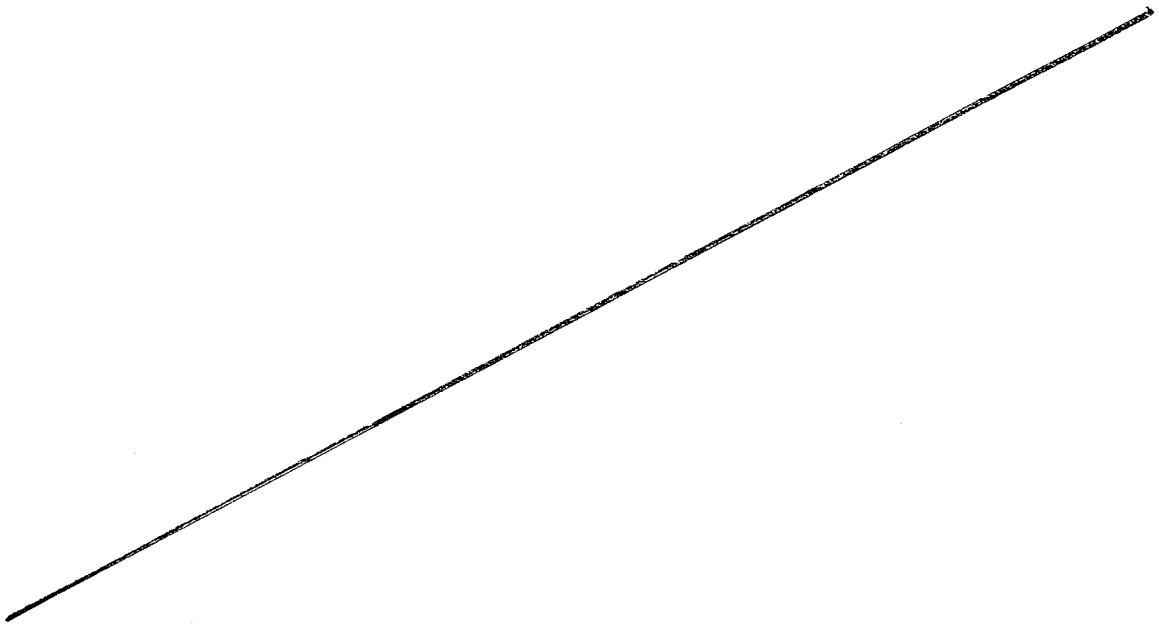
"In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. *The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.*

More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α).

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 CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether 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 SUTENT. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving***

SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered."

3. A subsection for **QT Interval Prolongation** has been added to the **WARNINGS AND PRECAUTIONS** section as follows:



b(4)

CSO Comment: This change was reviewed by the team and revised wording was recommended to the sponsor during labeling negotiations. The final agreed-upon language for this section is as follows:

"SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered [see Dosage and Administration (2.2)]."

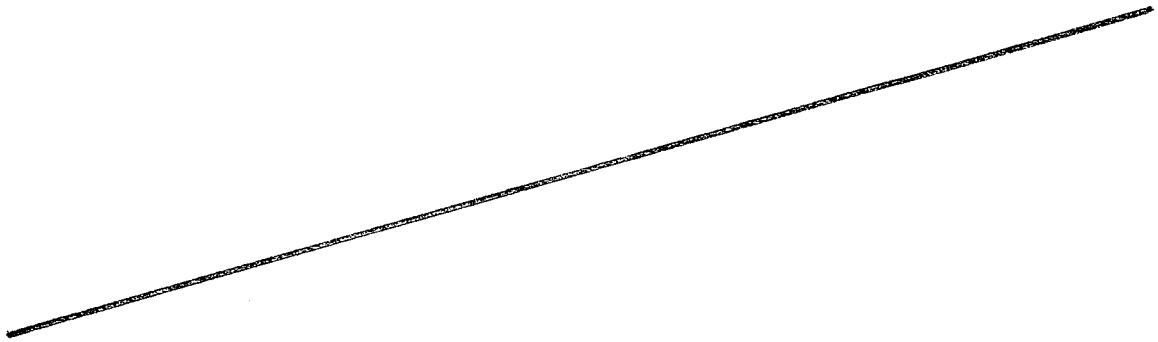
4. In the **WARNINGS AND PRECAUTIONS** section, the first paragraph in the **Hemorrhagic Events** subsection has been modified as follows (additions shown as underlined text):

"Bleeding events occurred in 37/202 patients (18%) receiving SUTENT in GIST Study A, compared to 17/102 patients (17%) receiving placebo. [redacted]

b(4)

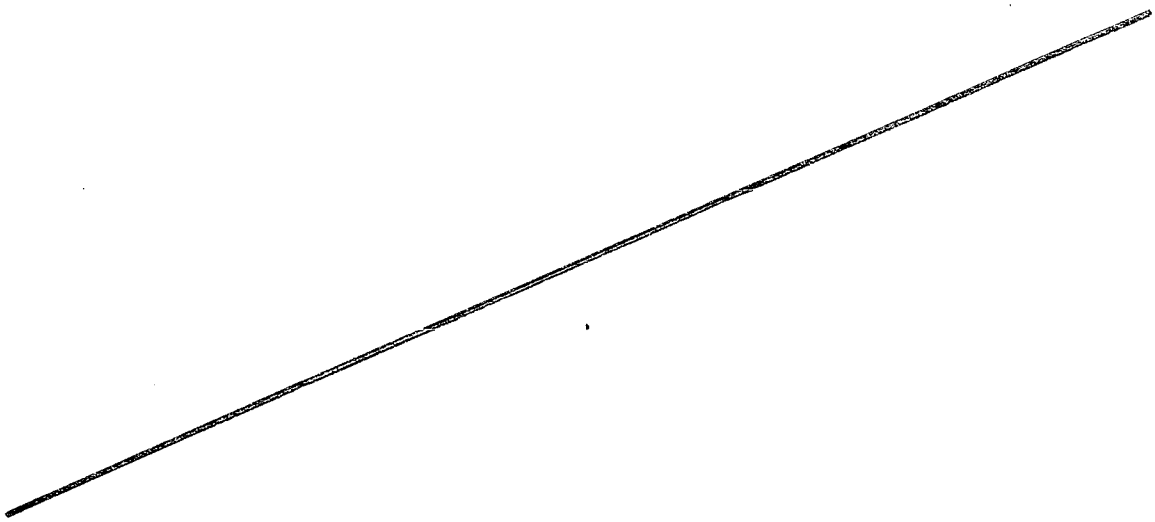
b(4)

CSO Comment: This change was reviewed by the team and revised wording was recommended to the sponsor during labeling negotiations. The final agreed-upon language for this paragraph is outlined below:



b(4)

5. In the **WARNINGS AND PRECAUTIONS** section, the **Hypertension** subsection has been modified as follows (additions shown as <u>underlined</u> text):



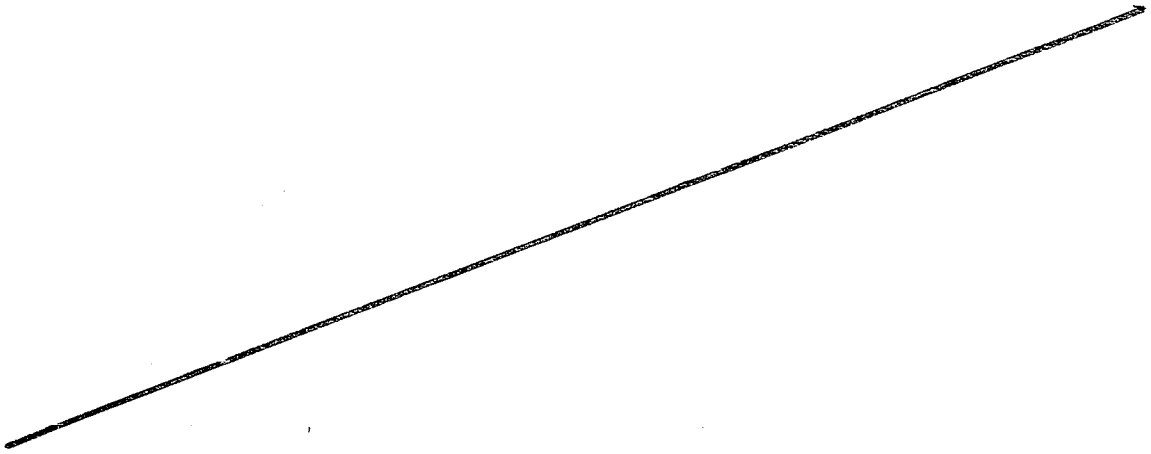
b(4)

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

CSO Comment: This change was reviewed by the team and revised wording was

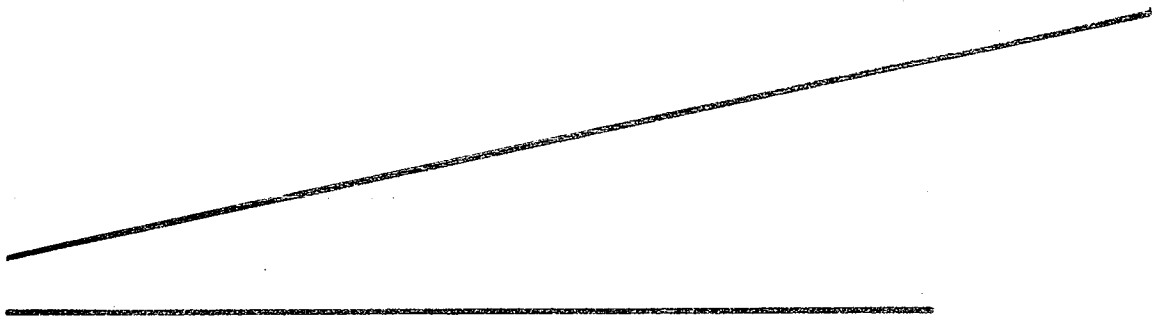
recommended to the sponsor during labeling negotiations. The final agreed-upon language for this section is as follows:

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



b(4)

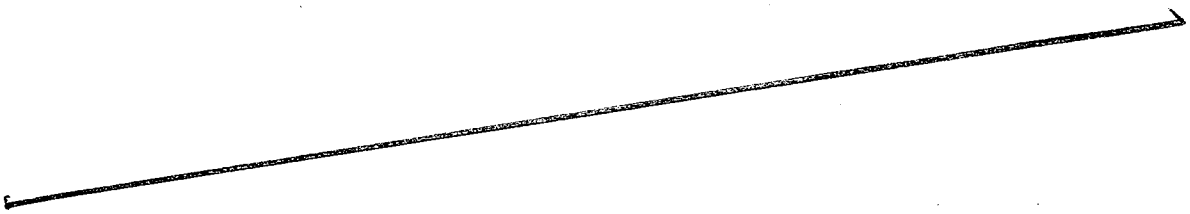
6. The **Overview** section of **ADVERSE REACTIONS** has been modified as follows:



b(4)

has been changed to

b(4)



b(4)

[redacted] b(4)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

CSO Comment: This change was reviewed by the team and revised wording for the second paragraph was recommended to the sponsor during labeling negotiations. The final agreed-upon language for the second paragraph is outlined below:

"The most common adverse reactions (≥20%) in patients with GIST or [redacted]RCC are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia, and bleeding. The potentially serious adverse reactions of left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, and adrenal function are discussed in Warnings and Precautions (5). Other adverse reactions occurring in GIST and MRCC studies are described below." b(4)

7. A new subsection titled **Adverse Events in the Treatment-Naïve MRCC Study** has been added as follows:

[redacted] b(4)

[redacted]

b(4)

Table 1. [redacted]

___1___ Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___√___ Draft Labeling (b4)

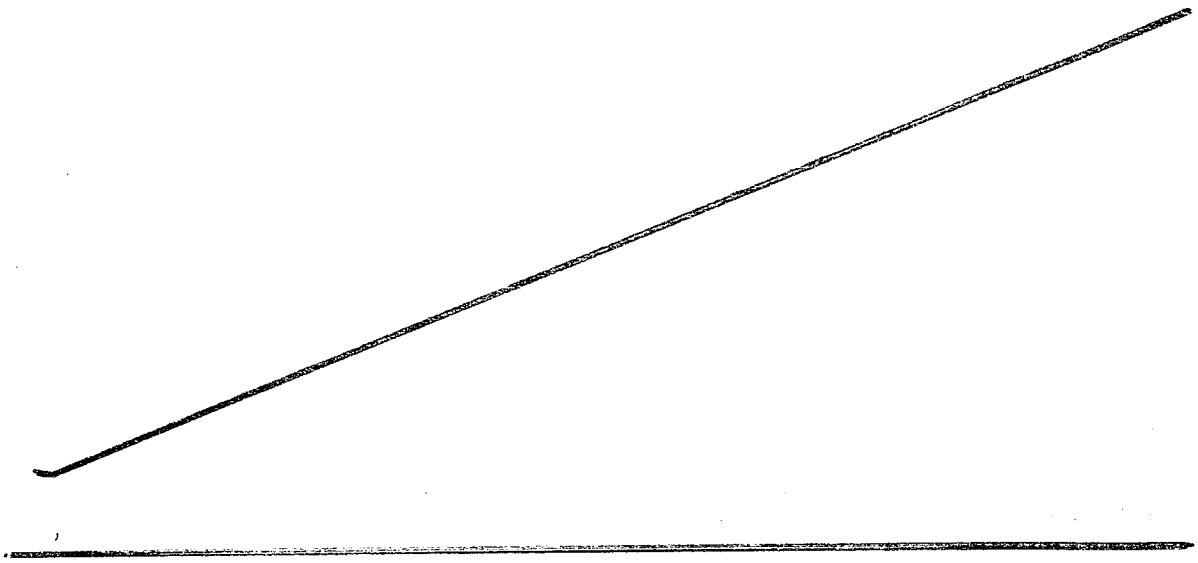
_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews-___1____

[e] Includes decreased appetite
[f] Includes one patient with non-treatment-related Grade 5 gastric hemorrhage

CSO Comment: This section was reviewed by the team and revisions were recommended to the sponsor during labeling negotiations. The final agreed-upon language for this section is as follows:



b(4)

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews- 2

*agreed that this section should be renamed "**Pancreatic and Hepatic Function**" and should be revised as follows:*

"If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve /RCC compared to 1 (<1%) patient receiving IFN-α. Hepatic failure was observed in <1% of solid tumor patients treated with SUTENT." b(4)

12. In the **USE IN SPECIFIC POPULATIONS** section, the **Geriatric Use** subsection has been revised as follows (additions shown as underlined text):

[redacted] b(4)

CSO Comment: This change was reviewed by the team and was found to be acceptable with the deletion of the word "[redacted]".

13. In the **USE IN SPECIFIC POPULATIONS** section, the **Hepatic Impairment** subsection has been revised as follows (additions shown as underlined text): b(4)

"Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN. [redacted] b(4)

CSO Comment: This change was reviewed by the team and revisions were recommended to the sponsor during labeling negotiations. The final agreed-upon text for this section is as follows:

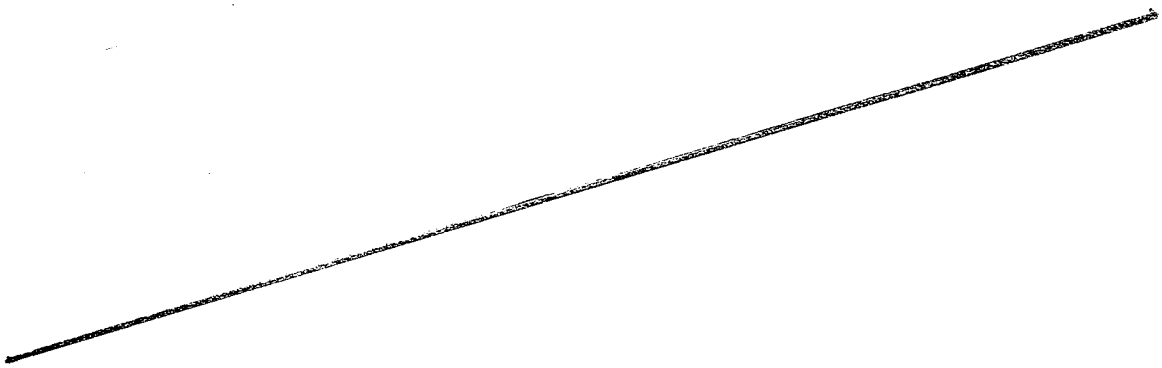
"No dose adjustment is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN."

14. In the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, a subsection titled *Hepatic Insufficiency* has been added under the *Pharmacokinetics in Special Populations* subheading as follows:

"Hepatic Insufficiency: Systemic exposures after a single dose of SUTENT were similar in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to subjects with normal hepatic function."

CSO Comment: This change was reviewed by the team and was found to be acceptable.

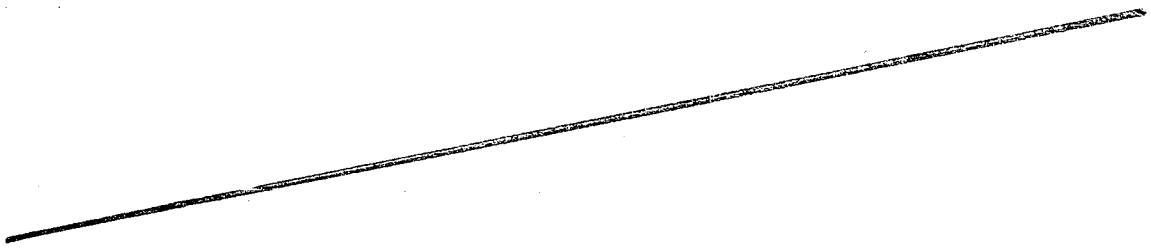
15. In the **CLINICAL STUDIES** section, the second paragraph in the **GIST Study A** subsection has been modified as follows (additions shown as underlined text):



b(4)

CSO Comment: This change was reviewed by the team and was found to be acceptable.

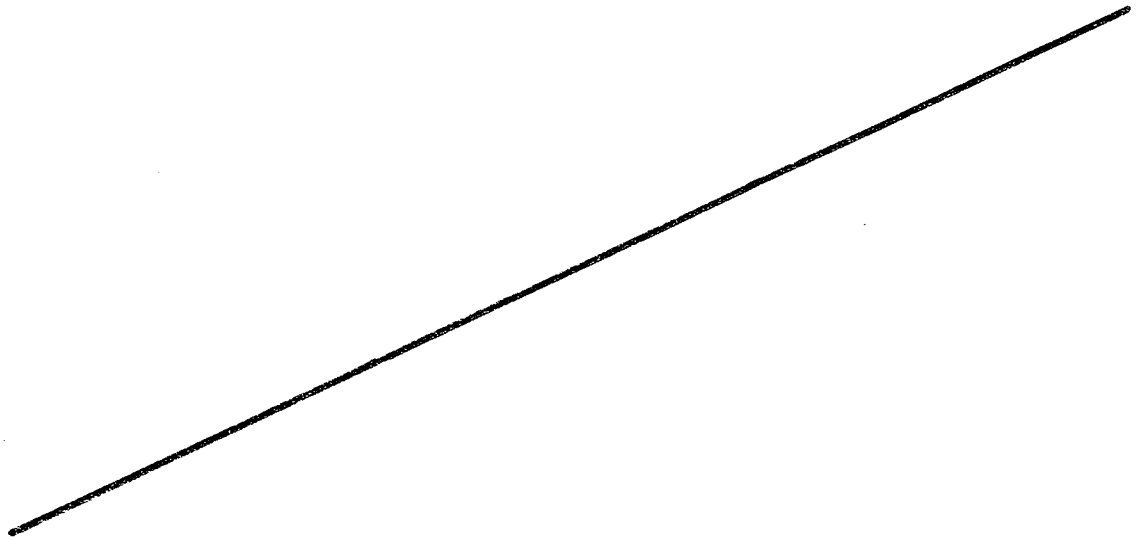
16. In the **CLINICAL STUDIES** section, a new subsection titled [redacted] has been added under the **Renal Cell Carcinoma** section as follows:



b(4)

[redacted] included 750 patients, 375 randomized to SUTENT and 375 randomized to IFN-α. Demographics were comparable between the SUTENT and IFN-α groups with regard to age (59% vs 67% < 65 years for SUTENT vs. IFN-α, respectively), gender (Male: 71% vs. 72%), race (White: 94% vs. 91%, Asian: 2% vs. 3%, Black: 1% vs. 2%, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%, ECOG 1: 38% each arm, ECOG 2: 0 vs. 1%). Prior treatment included nephrectomy (91% vs. 89%) and radiotherapy (14% each arm).

The most common site of metastases present at screening was the lung (78% versus 80%, respectively), followed by the lymph nodes (58% versus 53%, respectively) and bone (30% each arm); the majority of the patients had multiple (2 or more) metastatic sites at baseline (80% versus 77%, respectively).



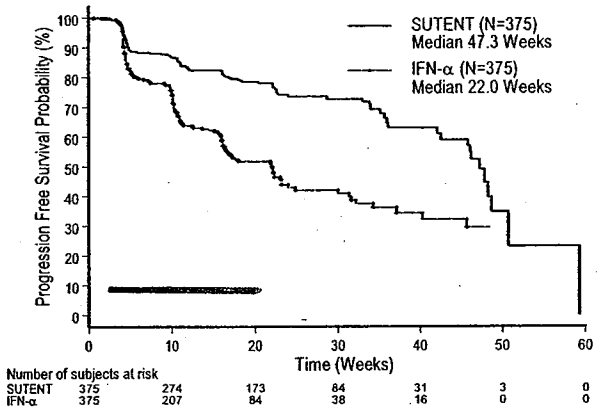
b(4)

Efficacy Parameter	SUTENT (n=375)	IFN-α (n=375)	P-value (log-rank test)	HR (95% CI)
Progression-Free Survival[a] [median, weeks (95% CI)]	47.3 (42.6, 50.7)	22.0 (16.4, 24.0)	<0.000001	0.415 (0.320, 0.539)
Objective Response Rate[a] [%, (95% CI)]	27.5 (23.0, 32.3)	5.3 (3.3, 8.1)	<0.0001	NA

b(4)

Figure 1. Kaplan-Meier Curve of PFS in Treatment-Naïve MRCC Study (Intent-to-Treat Population)

b(4)



b(4)

CSO Comment: This change was reviewed by the team. Revised wording was recommended to the sponsor during labeling negotiations. The final agreed-upon language for this section is as follows:

"A multi-center, international randomized study comparing single-agent SUTENT with IFN-α was conducted in patients with treatment-naïve MRCC. The objective was to compare Progression-Free Survival (PFS) in patients receiving SUTENT versus patients receiving IFN-α. Other endpoints included Objective Response Rate (ORR), Overall Survival (OS) and safety. Seven hundred fifty (750) patients were randomized (1:1) to receive either 50 mg SUTENT once daily on Schedule 4/2 or to receive IFN-α administered subcutaneously at 9 MIU three times a week. Patients were treated until disease progression or withdrawal from the study.

The ITT population for this interim analysis included 750 patients, 375 randomized to SUTENT and 375 randomized to IFN-α. Demographics were comparable between the SUTENT and IFN-α groups with regard to age (59% vs. 67% <65 years for SUTENT vs. IFN-α, respectively), gender (Male: 71% vs. 72%), race (White: 94% vs. 91%, Asian: 2% vs. 3%, Black: 1% vs. 2%, remainder not reported), and Performance Status (ECOG 0: 62% vs. 61%, ECOG 1: 38% each arm, ECOG 2: 0 vs. 1%). Prior treatment included nephrectomy (91% vs. 89%) and radiotherapy (14% each arm). The most common site of metastases present at screening was the lung (78% vs. 80%, respectively), followed by the

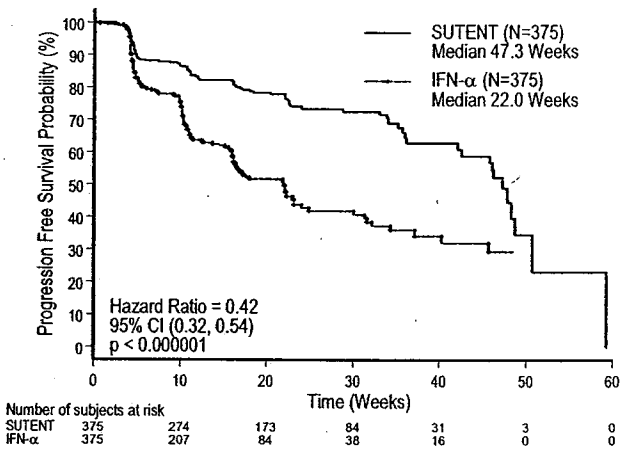
lymph nodes (58% vs. 53%, respectively) and bone (30% each arm); the majority of the patients had multiple (2 or more) metastatic sites at baseline (80% vs. 77%, respectively).

b(4)

Efficacy Parameter	*SUTENT (n=375)*	*IFN-α (n=375)*	*P-value (log-rank test)*	*HR (95% CI)*
Progression-Free Survival[a] [median, weeks (95% CI)]	*47.3 (42.6, 50.7)*	*22.0 (16.4, 24.0)*	*<0.000001[b]*	*0.415 (0.320, 0.539)*
Objective Response Rate[a] [%, (95% CI)]	*27.5 (23.0, 32.3)*	*5.3 (3.3, 8.1)*	*<0.001[c]*	*NA*

CI=Confidence interval, NA=Not applicable
[a] Assessed by blinded core radiology laboratory; 90 patients' scans had not been read at time of analysis
[b] A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)
[c] Pearson Chi-square test

Figure 2. Kaplan-Meier Curve of PFS in Treatment-Naïve MRCC Study (Intent-to-Treat Population)



17. The following **Reference** has been added:

b(4)

5 Page(s) Withheld

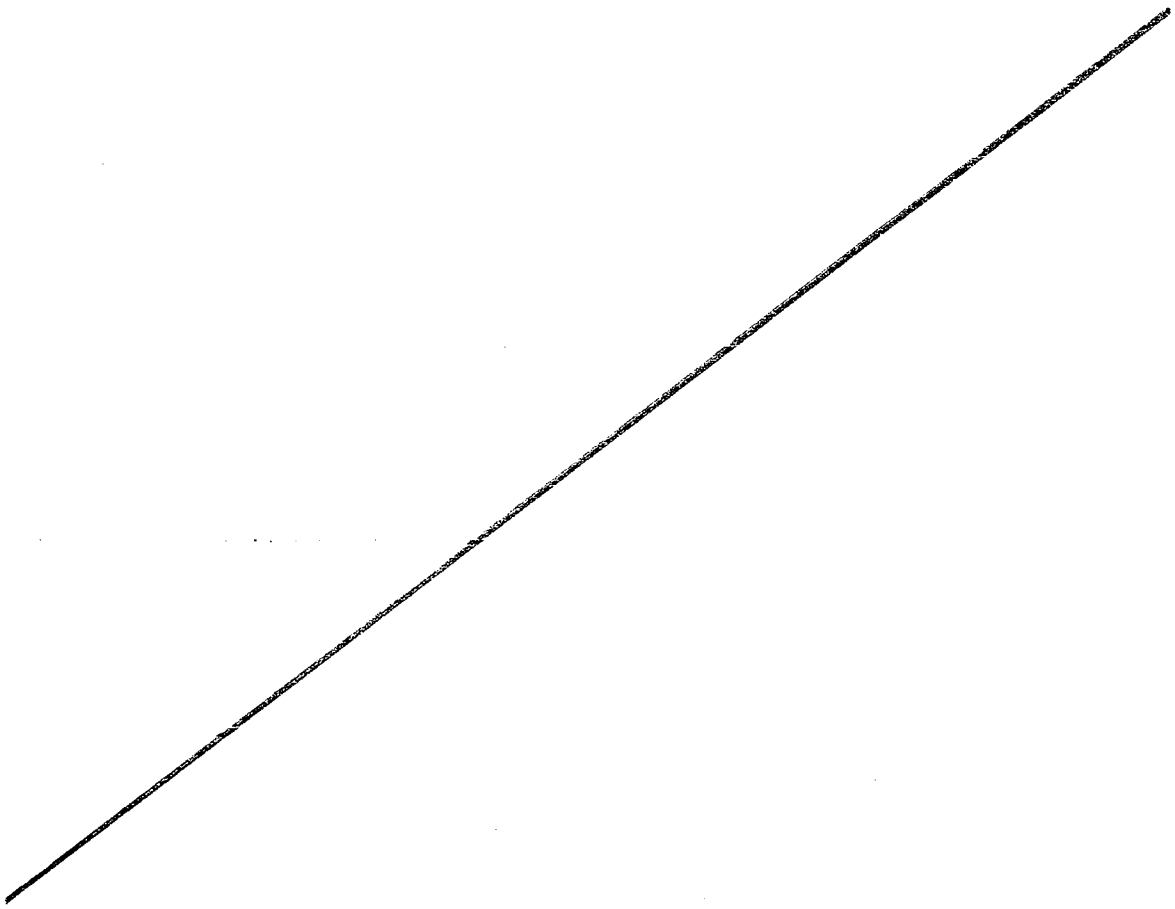
_____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews- 3



b(4)

19. During the initial Project Manager review of the labeling, specific PLR formatting issues were identified and conveyed in the 74-day Filing Letter. These deficiencies are outlined below.

Highlights

1. The Highlights section is too long. Please edit the contents of this section so it is no longer than half a page.

2. Please remove the ® symbol from the tradename immediately above the initial U.S. approval date.

3. Under Recent Major Changes, the heading, and if appropriate, subheading of the labeling section affected by the change, must be listed together. Therefore, it must read, "Indications and Usage, Advanced Renal Cell Carcinoma", not just "Indications and Usage". Please correct. In addition, the corresponding new or modified text under this section in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge.

4. Other than in the Recent Major Changes section, the corresponding sections of the FPI are not referenced anywhere else in Highlights. Please add these references.

5. Please remove the Pregnancy Category designation from the Warnings and Precautions section.

6. A summary of adrenal toxicity should be included under Warnings and Precautions.

7. The Adverse Reactions section should be updated to include only the most frequently occurring adverse reactions rather than all-causality adverse events.

8. The Adverse Reaction contact reporting statement in the Adverse Reactions section should be bolded.

Full Prescribing Information (FPI)

7. The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier [e.g., see *Indications and Usage (1.1)*]. Since cross-references are embedded in the text of the FPI, the use of italics to achieve emphasis is encouraged.

8. All identifying numbers must precede the heading or subheading by at least two square "ems" (i.e., two squares the size of the letter "m" in 8 point type).

9. In the Adverse Reactions section, you must include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials in which exposure occurred (e.g., placebo-controlled, active-controlled), and any critical exclusions from the safety database. Sample database description:

   "The data described below reflect exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo- and active-controlled trials (n=____, and n=____, respectively), and in long-term follow up studies. The population was [age range], [gender distribution], [race distribution], and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate]."

10. The Adverse Reactions section must also contain the standard statement: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice".

11. The Adverse Reactions section should contain only the controlled trial data, and should include only those events which occurred more frequently with Sutent than with placebo/IFN.

12. The Adverse Reactions section overview should contain a summary of frequent/important adverse reactions.

13. In the Use in Specific Populations section, the Hepatic Impairment subsection should be numbered 8.6 rather than 8.7. Please also revise the Contents section of the FPI to reflect this change.

14. In the Clinical Studies section, there are instances where the terms "primary" and "secondary" have been used to describe objectives. These should be removed.

15. In the Clinical Studies section, the demographics are presented in tabular format. Please delete the table and describe the demographics in text format indicating those criteria that are balanced or not. The demographic characteristics should generally be limited to the following: age, gender, race, performance status, disease characteristics (tumor type, stage), prior treatment, and predictors.

16. Please add a section 17.5 titled FDA-Approved Patient Labeling and attach the Patient Package Insert to the end of the FPI.

17. Manufacturer information should be located after the Patient Counseling Information section, at the end of the FPI. If the product will have FDA-approved patient labeling that is not a separate document or printed such that it is intended to be detached and distributed to patients, the manufacturer information should be located at the end of the labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling.

CSO Comment: These PLR format deficiencies have been addressed during labeling negotiations. Dr. Iris Masucci, of the Study Endpoints and Labeling Development (SEALD) team, completed a PLR format and content review. Her review can be found in DFS and is included in the action package for these supplements. All PLR content issues have also been addressed during labeling negotiations.

RECOMMENDATIONS:

An APPROVAL letter should issue for NDA 21-938/SLR-002, SE8-003/004/005 and NDA 21-968/SLR-002, SE8-003/004/006, and SE7-005. A separate ACKNOWLEDGE AND RETAIN letter should issue that states that the FPL submitted for both NDAs has been superseded.

Concurrence:

Christy Cottrell
Consumer Safety Officer

Frank Cross
Chief, Project Management Staff

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Cottrell
2/2/2007 04:08:23 PM
CSO

Frank Cross
2/2/2007 04:26:21 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-938 / S-002; 003; 004; 005

21-968 / S-002; 003; 004; 005; 006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-938 and 21-968 SUPPL # 003 (for both NDAs)

HFD # 150

Trade Name Sutent Capsules

Generic Name sunitinib malate

Applicant Name CP Pharmaceuticals International CV

Approval Date, If Known February 2, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-938

NDA# 21-968

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A Phase 3, Randomized Study of SU011248 versus Interferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A Phase 3, Randomized Study of SU011248 versus Interferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
IND # 62,382	YES ☒	! NO ☐ ! Explain:
Investigation #2		!
IND #	YES ☐	! NO ☐ ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐ Explain:	NO ☐ Explain:

Investigation #2 YES ☐ Explain:	 NO ☐ Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Christy Cottrell
Title: Consumer Safety Officer
Date: January 31, 2007

Name of Office/Division Director signing form: Robert L. Justice, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Christy Cottrell
2/8/2007 12:04:53 PM

Robert Justice
2/8/2007 05:32:12 PM

EXCLUSIVITY SUMMARY

NDA # 21-968 SUPPL # 004 HFD # 150

Trade Name Sutent Capsules

Generic Name sunitinib malate

Applicant Name C.P. Pharmaceuticals International CV

Approval Date, If Known February 2, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-938

NDA# 21-968

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A Pivotal Study of SU 011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

A Pivotal Study of SU 011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma (NDA 21-968)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

None

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

Investigation #2 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 !

YES ☐ ! NO ☐

Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Christy Cottrell
Title: Consumer Safety Officer
Date: January 31, 2007

Name of Office/Division Director signing form: Robert L. Justice, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Cottrell
2/8/2007 11:11:25 AM

Robert Justice
2/8/2007 05:37:28 PM

EXCLUSIVITY SUMMARY

NDA # 21-938 and 21-968 SUPPL # 004 and 005, respectively

HFD # 150

Trade Name Sutent Capsules

Generic Name sunitinib malate

Applicant Name C.P. Pharmaceuticals International CV

Approval Date, If Known February 2, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE7

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-938

NDA# 21-968

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A Phase 3, Randomized Study of SU011248 versus Inteferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

A Phase 3, Randomized Study of SU011248 versus Inteferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma (NDA 21-968)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

None

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐ Explain:	! NO ☐ ! Explain:
Investigation #2 YES ☐ Explain:	! ! ! NO ☐ ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Christy Cottrell
Title: Consumer Safety Officer
Date: January 31, 2007

Name of Office/Division Director signing form: Robert L. Justice, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Christy Cottrell
2/8/2007 11:55:04 AM

Robert Justice
2/8/2007 05:34:16 PM

EXCLUSIVITY SUMMARY

NDA # 21-938 and 21-968 SUPPL # 005 and 006, respectively

HFD # 150

Trade Name Sutent Capsules

Generic Name sunitinib malate

Applicant Name C.P. Pharmaceuticals Internation CV

Approval Date, If Known February 2, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This is a study in hepatically-impaired subjects and shows that the pharmacokinetics of the drug is not altered in patients with hepatic impairment.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-938

NDA# 21-968

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A Phase I Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A Phase I Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 62,382	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Christy Cottrell
Title: Consumer Safety Officer
Date: January 31, 2007

Name of Office/Division Director signing form: Robert L. Justice, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Christy Cottrell
2/8/2007 11:49:56 AM

Robert Justice
2/8/2007 05:36:00 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #/Supplement Types and Numbers (e.g., SE5) and Stamp Dates and Therapeutic Class:

NDA 21-938 SE8-003 (August 1, 2006) **[S]**; SE8-004 and SE8-005 (August 9, 2006) **[P]**
NDA 21-968 SE8-003 and SE8-004 (March 31, 2006) **[S]**; SE7-005 and SE8-006 (August 9, 2006) **[P]**

HFD-150__ **Trade and generic names/dosage form:__**Sutent (sunitinib malate) Capsules_

Applicant: C.P. Pharmaceuticals International C.V.

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ❑ **Yes. Please proceed to the next question.**
- **X No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only):_____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s):_____

Indication #1: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

[See appended electronic signature page]

Christy Cottrell
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Christy Cottrell
1/19/2007 03:15:13 PM

From: Cottrell, Christy
Sent: Wednesday, February 07, 2007 2:10 PM
To: 'Strawn, Laurie'
Subject: NDA 21-938 and NDA 21-968

Laurie,

Please refer to your NDAs 21-938 and 21-968 for SUTENT (sunitinib malate) Capsules. See below for a comment from the clinical pharmacology reviewer.

- We do not believe that you have observed the maximum QT prolongation for SUTENT in your QT study (A6181005), since ECGs were collected only up to 24 hours on days 3 and 9. We recommend that you develop an ECG sampling plan to assess the maximum effect of the drug on the QT interval, as part of your current/future studies.

Feel free to contact me if you have any questions.

Thanks,
Christy

****

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Cottrell
2/7/2007 02:15:40 PM
CSO

Cottrell, Christy

From: Strawn, Laurie [laurie.strawn@pfizer.com]
Sent: Thursday, February 01, 2007 1:18 PM
To: Cottrell, Christy
Subject: RE: Post-marketing commitments for SUTENT

Hi Christy,

We approve of the post-marketing commitments. As discussed yesterday, the final CSR for #1 below is expected February 2009. For #9, we expect the final CSR in December 2007.

I am still awaiting for a few of the managers to approve the label, but I have urgent messages out to all of them.
Laurie

From: Cottrell, Christy [mailto:christy.cottrell@fda.hhs.gov]
Sent: Wednesday, January 31, 2007 9:02 AM
To: Strawn, Laurie
Subject: Post-marketing commitments for SUTENT

Laurie,

We converted PMC #5 to a regular PMC as requested. In addition, for PMC #2 (fulfilled with this supplement), since the overall survival data and duration of response data are not mature, we need to make a new regular PMC for their submission.

See below.

1. Provide the complete study report and datasets with the final definitive statistical analysis of overall survival and duration of response for the study titled, "A Phase 3, Randomized Study of SU011248 versus Interferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

   Protocol Submission: submitted 6/2004
   Study Start: 8/2004
   Final Report Submission: TBD

Let me know if you agree with this PMC as written and please provide a date for final report submission.

One other thing....For PMC #9 (see below), the study report submission date is listed as 12/2006. Can you provide a new estimated date for submission of this report? (Note that it won't change the "delayed" status of the PMC, but it will give us an idea of when to expect it).

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".

   Protocol Submission: submitted 11/2003
   Study Start: 12/2003

Final Report Submission: by 12/2006*

Thanks,
Christy

****

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-968	Supplement # 005/006	Efficacy Supplement Type SE-	7 and 8, respectively

Proprietary Name: Sutent Capsules
Established Name: sunitinib malate
Strengths: 12.5 mg, 25 mg, 50 mg sunitinib equivalent

Applicant: C.P. Pharmaceuticals International C.V.
Agent for Applicant (if applicable): Pfizer, Inc.

Date of Application: August 9, 2006
Date of Receipt: August 9, 2006
Date clock started after UN: n/a
Date of Filing Meeting: October 3, 2006
Filing Date: October 10, 2006
Action Goal Date (optional): February 2, 2007 User Fee Goal Date: February 11, 2007

Indication(s) requested: no new indication

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) n/a
Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐

  If yes, explain: original NDAs 21-938 and 21-968 still under 5-year exclusivity at time of supplement submission

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☒
     This application is: All electronic ☒ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☒
     Combined NDA and CTD formats ☐

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

     Additional comments:

  3. This application is an eCTD NDA. YES ☒

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒
- PDUFA and Action Goal dates correct in tracking system? YES ☐ NO ☒
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes
- List referenced IND numbers: IND 62,382
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) n/a NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) n/a NO ☒
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) n/a NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☒

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? n/a
  YES ☐ NO ☐

Chemistry

n/a

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

NO FILING MEETING HELD

DATE: October 3, 2006

NDA #: 21-968/S-005/S-006

DRUG NAMES: Sutent (sunitinib malate) Capsules

APPLICANT: C.P. Pharmaceuticals International C.V.

BACKGROUND: These supplements contain final study reports for the following studies:

"A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma" and "A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function"

These study reports were submitted in fulfillment of post-marketing commitments from the January 26, 2006 approval of Sutent. Labeling revisions are proposed.

ATTENDEES: Christy Cottrell
Shenghui Tang, PhD
Jennie Chang, PharmD (observer)
Vicki Goodman, MD
Ramzi Dagher, MD
Amna Ibrahim, MD
Brian Booth, PhD
Robert Justice, MD
David Morse, PhD

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Vicki Goodman, MD
Secondary Medical:	Amna Ibrahim, MD
Statistical:	Shenghui Tang, PhD
Pharmacology:	Leigh Verbois, PhD (PLR labeling only)
Statistical Pharmacology:	n/a
Chemistry:	Liang Zhou, PhD (PLR labeling only)
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Roshni Ramchandani, PhD
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	n/a
OPS:	n/a

Regulatory Project Management: Christy Cottrell
Other Consults: DDMAC, SEALD, DSRCS, IRT

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: Not needed- no new indication sought
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY n/a ☐ REFUSE TO FILE ☐
FILE

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional): PLR formatting

issues

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Christy Cottrell
Regulatory Project Manager

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/s/

Christy Cottrell
1/31/2007 02:48:27 PM
CSO

MEMORANDUM OF TELECON

DATE: November 2, 2006

APPLICATION NUMBER: NDA 21-968/SE7-005 for Sutent (sunitinib malate) Capsules

BETWEEN:

Name: Laurie Strawn, PhD, Regulatory
Darrel Cohen, MD, Clinical
Isan Chen, MD, Clinical
Sindy Kim, MD, Clinical
Randy Allred, PhD, Statistics
Bob Ryan, PhD, Statistics
Zuleima Aguilar, Team Leader

Representing: C.P. Pharmaceuticals International C.V. (c/o Pfizer, Inc.)

AND

Name: Christy Cottrell, Consumer Safety Officer
Amna Ibrahim, MD, Acting Clinical Team Leader
Vicki Goodman, MD, Clinical Reviewer
Rajeshwari Sridhara, PhD, Statistical Team Leader
Shenghui Tang, PhD, Statistical Reviewer
S. Leigh Verbois, PhD, Pharm/Tox Reviewer

Representing: Division of Drug Oncology Products

SUBJECT: Clarify comments on draft labeling and which data included in PFS analysis

BACKGROUND:

On October 24, 2006, the Division issued a filing letter for NDA 21-968/S-005 and S-006. The filing letter contained initial comments on the format of the sponsor's proposed Physician's Labeling Rule (PLR) labeling. This telecon was requested by the sponsor to clarify several of the labeling comments contained in the filing letter.

In addition, the Division wanted to clarify which data were included in the PFS analysis.

DISCUSSION:

Labeling

Original FDA Comment #5:

Please remove the Pregnancy Category designation from the Warnings and Precautions section in Highlights.

Pfizer Questions:
1a. Is the intent to remove the Pregnancy Category designation completely from the Highlights, or, in view of the severity of the D designation, should it be moved to the Use in Specific Populations section of the Highlights?

FDA REPLY: We are only requesting that the designation (i.e., "D") be removed. The text should remain. The "D" is not informative.

1b. If the Pregnancy Category designation should be moved in the Highlights, should it also be moved in the Full Prescribing Information to the Use in Specific Populations section, as described in Appendix C of draft "Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (January 2006)"?

FDA REPLY: Refer to the recently approved Zolinza label. You should include a cross-reference to Warnings and Precautions anywhere the Pregnancy Category designation is mentioned.

Original FDA Comment #7

The Adverse Reactions section should be updated to include only the most frequently occurring adverse reactions rather than all-causality adverse events.

Pfizer Question: *The current draft labeling lists all-causality adverse reactions occurring in ≥20% of patients (n=577) and the most common laboratory abnormalities. Please clarify your definition of "the most frequently occurring adverse reactions" and whether or not this section should additionally include laboratory abnormalities.*

FDA REPLY: In Highlights, you should include adverse reactions occurring in >20% of patients that are drug related. Laboratory data do not belong in Highlights. The Full Prescribing Information will be changed to reflect only treatment-related adverse reactions.

Original FDA Comment #11

The Adverse Reactions section should contain only the controlled trial data, and should include only those events which occurred more frequently with Sutent than with placebo/IFN.

Pfizer Question: *Pfizer agrees to remove the adverse events data for cytokine-refractory metastatic renal cell carcinoma (MRCC) patients from Table 3 of the draft labeling since these data were from uncontrolled studies and the data are consistent between the treatment-naïve and cytokine-refractory MRCC populations.*

Pfizer requests guidance for the removal of data to address the request to only report the events that are more frequent on Sutent than placebo/IFN. "Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006)" defines "most commonly occurring adverse reactions" as "all adverse reactions occurring at a rate of 10 percent or greater in the treatment group and at a rate at least twice the placebo rate". In view of the high rate of adverse events in cancer patients regardless of treatment received, strictly applying this definition would result in the removal of most of the events in Tables 1 and 3, which in the draft labeling report events occurring in at least 10% of patients without comparing the arms. If only events occurring at twice the rate in the Sutent arm are included, important events such as diarrhea, hypertension and bleeding will be removed from the GIST adverse event table. Furthermore, in the case of the treatment-naïve MRCC study, retaining the adverse events that are higher on the interferon arm allows healthcare providers to make an informed decision regarding treatment options. Does the Agency agree that alternate criteria should be applied to determine which adverse events should be retained in this section?

> **FDA REPLY:** This will be a review issue. We will look at all grades as well as grade 3/4. The laboratory abnormalities table can stay in the labeling. Anything treatment related should stay.

Data for PFS Analysis

The Division asked the sponsor to clarify which data were included in the PFS analysis. The sponsor explained that for patients with an event of progression or death, the date of the event (e.g., progression or death occurring "on study") was the failure date. The sponsor went on to explain that patients with no post-baseline assessments were censored on the day of randomization. Finally, for patients who completed treatment and were alive without evidence of progression (or who received additional anti-cancer therapy without documentation of progression), censoring occurred on the day following the last day of treatment.

The telecon concluded at 12:30pm.

_____

Christy Cottrell
Consumer Safety Officer

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/s/

Christy Cottrell
1/29/2007 12:19:11 PM

Division of Drug Marketing, Advertisement, and Communications

Comments discussed during labeling meeting (1/31). CC

Internal Consult

****Pre-decisional Agency Information****

To: Vicki Goodman, MD, Medical Officer, DDOP
Christy Cottrell, Project Manager, DODP

From: Kathy Oh, Regulatory Review Officer, DDMAC

CC: Mark Askine, Associate Director, DDMAC
Andy Haffer, Regulatory Review Officer, DDMAC
Joseph A. Grillo, Regulatory Review Officer, DDMAC
Iris Masucci, Labeling Reviewer, DDMAC

Date: January 24, 2007

Re: NDA # 21-968
Sutent™ (Sunitinib Malate) Capsules
Comments on draft Labeling

In response to your consult request via email on January 12, 2007, we have reviewed the draft Labeling (draft version that was sent on January 24, 2007) and offer the following comments:

Section	Statement from draft	Comment
5.5 Hemorrhagic Events – first paragraph	[redacted]	Considering the incidence of bleeding events is 30% for patients receiving SUTENT for treatment-naïve MRCC, this claim could be used promotionally to minimize the incidence of the more severe risks associated with Sutent, such as bleeding. We recommend omitting this statement.
6.1 Adverse Reactions in GIST	"Most treatment-emergent adverse reactions in both study arms were Grade	This claim could be used promotionally to minimize the risks associated with

b(4)

Section	Statement from draft	Comment
Study A – second paragraph 6.2 Adverse Events in the Treatment-Naïve MRCC Study – first paragraph	1 or 2 in severity.	SUTENT. Considering the table that follows provides the incidence rates for the adverse events for all grades, is it necessary to include this statement that is promotional in tone? If not, we recommend omitting this statement.
Table 1	Adverse Reactions Reported in at Least 10% of Patients with MRCC Who Received SUTENT	The data in the table is based on an interim safety analysis. Is it important to indicate this information in the header of Table 3 in a similar manner as it appears for Table 4 and 5? If so, we recommend including this information in the header of the table.

b(4)

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/s/

Kathy Oh
1/25/2007 10:48:14 AM
DDMAC REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-938/S-004/S-005
NDA 21-968/S-005/S-006

PRIOR APPROVAL SUPPLEMENT

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Laurie M. Strawn, Ph.D.
Director, Worldwide Regulatory Strategy

Dear Dr. Strawn:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Sutent (sunitinib malate) Capsules 12.5 mg, 25 mg, 50 mg sunitinib equivalent
NDA Numbers:	21-938 and 21-968
Supplement numbers:	004/005 and 005/006, respectively
Review Priority Classification:	Priority (P)
Date of supplement:	August 9, 2006
Date of receipt:	August 9, 2006

These supplemental applications provide for revisions to the labeling based on final study reports from the following studies: "A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma" and "A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function". These study reports were submitted in fulfillment of post-marketing commitments from the January 26, 2006 approval of Sutent.

This application was filed on October 10, 2006, in accordance with 21 CFR 314.101(a). The user fee goal date is February 11, 2007.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the application numbers listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Cottrell
1/19/2007 03:03:23 PM

Discussed during Labeling negotiations. (cc)

MEMORANDUM

To: **Christy Cottrell**
Division of Drug Oncology Products

From: **Iris Masucci, PharmD, BCPS**
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **January 18, 2007**

Re: **Comments on draft labeling for Sutent (sunitinib) capsules**
NDA 21-968/SE7-005

We have reviewed the proposed label for Sutent (FDA version dated 1/9/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Throughout the label, the renal cell carcinoma (RCC) use is sometimes called "advanced RCC" and sometimes "metastatic RCC." Please select one term and use it throughout the label for consistency.

- When doses are described in the label, sometimes there is a hyphen between the strength and the units (e.g., 25-mg). In an effort to reduce potential medication errors, the current recommendation is to use just a space when expressing doses (e.g., 25 mg). Please correct throughout the label.

- Throughout the safety sections of the label, the term "adverse events" is commonly used. Where appropriate, please change to "adverse reactions." For further explanation, please see the guidance on Adverse Reactions, which clearly defines the differences in these two terms and what should be included in labeling.

- The section on Adverse Reactions includes subsections on venous thromboembolic events, leukoencephalopathy, and hypothyroidism. Are any (or all) of these important enough to warrant moving them to Warnings and Precautions? They may be overlooked if presented in their current place, following the standard adverse event tables.

- Throughout the label, subheadings that are not numbered (e.g., under 6.8 Laboratory Abnormalities) should not be in bold type. We recommend underlining and italicizing for

such section headings. Bold headings are reserved for numbered sections and subsections. Please correct throughout the label.

- Many of the cross-references in both the Highlights and Full Prescribing Information (FPI) appear in blue type on the computer screen. Please ensure the font is all black throughout. Also, all cross-references in the FPI should use this formatting: *[see Clinical Pharmacology (12.3)]*.

HIGHLIGHTS

Recent Major Changes

- For each entry in this section, the corresponding date should be the date of the label change. Please ensure that these dates are correct.

- The new text in the FPI that reflects each of these changes must have a vertical mark in the left margin.

Dosage and Administration

- For ease of reading, we recommend that each item here be its own bullet rather than presenting the information in one paragraph.

b(4)

- [redacted]

The wording of this sentence seems imprecise. We recommend, "Increase or decrease doses in 12.5 mg increments based on individual patient requirements" or something similar. Please note that the same sentence appears under "2.2 Dose Modifications" in the FPI.

Contraindications

- A cross-reference to section 4 (in parentheses) should be added after "None."

Warnings and Precautions

- Please evaluate the Warnings and Precautions listed here to ensure that they are in decreasing order of public health significance. Is the pregnancy warning the most important?

- In the second bullet about left ventricular ejection fraction decreases, should a mention of a potential need for dose reduction or discontinuation be added?

Adverse Reactions

- This list of common reactions is longer than is usually presented in Highlights. We generally see 5 or 6 reactions included here. This change will probably necessitate altering the cut-off value used here.

- Please delete the parentheses around the Pfizer telephone number in the adverse reactions contact information section.

Drug Interactions

- For clarity, please add "of SUTENT" to each of the bullets listed here (i.e., "Consider dose reduction of SUTENT when administered...") for clarity.

- Please add a second cross-reference in each bullet to the Pharmacokinetics section (12.3), where the drug interaction data appear.

Patient Counseling Statement

- Is the patient labeling that appears at the end "approved patient labeling"? If not, this statement should read simply, "See 17 for PATIENT COUNSELING INFORMATION."

Revision Date

- Please ensure that the revision date at the end of Highlights reflects the month/year of this label's approval.

CONTENTS

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.

- The title of section 5.1 should be changed from "Pregnancy Category D" to just "Pregnancy" both here and in the FPI. We are trying to get away from listing the pregnancy categories in isolation.

- The headings for sections 6.6 and 6.7 need fixing.

FULL PRESCRIBING INFORMATION

2.2 Dose Modification

- *"Strong CYP3A4 inhibitors such as ketoconazole may increase SUTENT plasma concentrations (see DRUG INTERACTIONS [7]). Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended."*

  We recommend that this portion of this paragraph be moved to "7 Drug Interactions," leaving only the last sentence, which should then cross-reference to the fuller discussion under the Drug Interactions and the Pharmacokinetics sections.

- *"CYP3A4 inducers such as rifampin may decrease SUTENT plasma concentrations (see DRUG INTERACTIONS [7]). Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended."*

  As above, we recommend this portion be moved to "7 Drug Interactions." What should remain here are the two middle sentences, "A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity," followed by a cross-reference to Drug Interactions and Pharmacokinetics.

- *"St. John's Wort may decrease SUTENT plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly."*

  This section does not belong under Dosage and Administration and should be moved to "7 Drug Interactions." Also, please consider if this interaction should be noted in the Highlights discussion of CYP3A4 inducers.

3 Dosage Forms and Strengths

- The descriptions of the capsules' appearances should be added here, repeating the information from "How Supplied/Storage and Handling" (without the NDC numbers or bottle sizes).

5.1 Pregnancy Category D

- Please consider switching the order of the two paragraphs in this section. The second paragraph is the more relevant information for the prescriber, which can then be followed by the animal data supporting it. This ordering is the preferred presentation by the Maternal Health Team of OND.

5.2 Left Ventricular Dysfunction

- As recommended in the pregnancy warning, we suggest that the overall clinical recommendations be presented first, followed by the supporting data. This would mean putting current paragraphs 2 and 3 first, followed by the current paragraph 1.

-

b(4)

We suggest deletion of all the incidence rates in parentheses in these sentences. The actual numbers are so small that these rates are somewhat meaningless and potentially misleading.

- For ease of reading, we suggest that the new information beginning with, "In the treatment-naïve MRCC study..." begin a new paragraph rather than continuing the paragraph on findings in the GIST study.

- *"In the treatment-naïve MRCC study, 78 (21%) and 44 (12%) patients on SUTENT and IFN-a, respectively, had an LVEF value below the LLN."*

  We suggest that the denominators for each patient group be added here for accuracy, e.g., "... 78/XX (21%) and 44/XX (12 %)..."

5.3 QT Interval Prolongation

- As above, please consider moving the clinical recommendations to the beginning of this section. These would begin with the sentence, "SUTENT should be used with caution in patients with a know history of..."

5.5 Hypertension

- *"While all-grade hypertension was similar in GIST patients on SUTENT compared to placebo; Grade 3 hypertension was reported in 9/202 GIST patients on SUTENT (4%), and none of the GIST patients on placebo."*

  The semi-colon in this sentence should be changed to a comma.

- As with the other Warnings, please consider moving the last paragraph to the beginning of the section.

5.6 Adrenal Function

- We again recommend that the last paragraph be moved to the beginning of this section.

- *"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."*

  We suggest moving this information to the new PLR section, "13.3 Animal Toxicology and/or Pharmacology" where preclinical data should appear. In its place, a sentence could appear here similar to, "Adrenal toxicity was noted in animals receiving SUTENT *[see Nonclinical Toxicology (13.2)]*."

6 Adverse Reactions

- We note that in many parts of this section, information from the currently approved labeling about adverse reactions in the cytokine-refractory MRCC patients has been deleted. Was this intentional? Please verify that no important information has been omitted.

6.1 Overview

- We recommend that this subsection heading be deleted. All of the general information that appears here can follow immediately under the heading "6 Adverse Reactions" without its own subheading. In general, vague section headings such as "Overview" and "General" should be avoided in labeling. The current 6.2 would now become 6.1.

- As in Highlights, this listing of "most common adverse reactions" is rather long. Please revise accordingly.

6.2 Adverse Reactions in GIST Study A

- *"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."*

  We recommend that this paragraph appear after Table 1, rather than before it. With this change, the table will appear immediately after it is introduced in the preceding paragraph.

- Table 2

  Within each body system in the table, adverse reactions should be listed in decreasing order of frequency.

6.3 Adverse Events in the Treatment-Naïve MRCC Study

- We suggest that the current second and third paragraphs in this section be moved to follow Table 3, so the table appears immediately after its introduction in the text.

- [redacted] b(4)

  Is this "Phase 3 MRCC study" the study of 735 patients? If so, please describe it another way to avoid confusion for the reader.

- Table 3

  This table shows only the adverse reactions that were more common with Sutent than with interferon-a. In a placebo-controlled trial, adverse reactions that were more

common with placebo than drug should not be included in the table. In an active-controlled trial, however, adverse reactions that occurred in either arm (above a specified rate) should usually be included in the table. Please see the Gleevec label for an example (in which Gleevec was compared to a combination arm of IFN+Ara-C). If you feel that a misleading safety advantage could be inferred from the presentation, then explanatory language could be added.

Within each body system, adverse reactions should be listed in decreasing order of frequency.

6.4 Cardiovascular Events

- This entire section should be deleted because it appears under Warnings and Precautions.

6.5 Venous Thromboembolic Events

- We suggest that the new information (beginning with "Eight (2%) patients receiving SUTENT for treatment-naïve MRCC...") begin a new paragraph.

6.6 Reversible Posterior Leukoencephalopathy Syndrome

- *"There have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS)."*

  Are these reports from postmarketing reporting or were they from the clinical trials? We presume they are from the trials because an incidence rate is given. Can the absolute number be given here? If there is postmarketing information on this, it should appear in a separate section on postmarketing experience after the clinical trials experience section.

6.8 Laboratory Abnormalities/ [redacted] b(4)

- We suggest that [redacted] be taken out of this section title. Any recommendations for laboratory testing for monitoring patients should appear in Warnings and Precautions, not under Adverse Reactions.

- Under "Hematologic Events," please delete any information that is redundant with the study adverse reaction descriptions (currently under 6.2 and 6.3).

- The "Hematologic Events" paragraph bounces back and forth between findings from the GIST studies and the MRCC studies, making it rather difficult to follow. Please revise to improve flow.

- [redacted] b(4)

  Please delete this sentence from the Adverse Reactions section.

- Is the subheading '[redacted]' the best title for this section? Would "Pancreatic and Hepatic Changes" or something similar be more accurate? b(4)

- *"If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued [redacted]."*

  Based on this sentence, should the risk of pancreatic and hepatic changes be a Warning/Precaution?

7 Drug Interactions

- Some of the information presented in this section belongs in "12.3 Pharmacokinetics" under a "Drug Interactions" subheading. The section "7 Drug Interactions" should give the clinical recommendations relating to the interactions (e.g., need for dosage adjustments, timing of administration, etc.). The actual pharmacokinetic data should appear only in the Pharmacokinetics section. Therefore, we recommend that this section be revised as follows: Section 7.1 would now be "CYP3A4 Inhibitors," and include the sentences beginning with, "Co-administration of SUTENT with strong inhibitors..." An additional cross-reference to 12.3 would then direct the reader to the PK data. Similarly, section 7.2 would now be "CYP3A4 Inducers," and would also begin with "Co-administration..." and a cross-reference. The first sentences originally in each section should be moved to PK. The paragraph under the original 7.1 heading would be moved as well.

8.1 Pregnancy

- The formatting of the cross-reference to Warnings and Precautions needs correcting.

8.3 Nursing Mothers

- In the first sentence, please change [redacted] to "and." b(4)

8.4 Pediatric Use

- The entire section paragraph in this section should be moved to "13.2 Animal Pharmacology and/or Toxicology." What would remain in 8.4 is the initial sentence about safety and efficacy not being studied in children, and then a second sentence summarizing the animal findings, with a cross-reference to 13.2 (e.g., "Animal studies have found evidence of... *[see Nonclinical Toxicology (13.2)]*" or something similar).

10 Overdosage

- *"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."*

As under "Pediatric Use," all animal data should be moved to Nonclinical Toxicology. A sentence can be added here that points the reader to the information in 13.2, with a cross-reference. The Overdosage section should include information on signs/symptoms of toxicity, as well as management recommendations.

14.2 Renal Cell Carcinoma

- Please change this heading to "Advanced" or "Metastatic" RCC to be consistent with the rest of the label.

- *"Other endpoints included Overall Response Rate (ORR), and Overall Survival (OS) safety."*

  Shouldn't the word "safety" be deleted from the end of this sentence?

- The second paragraph (beginning, "The ITT population for this interim analysis included 750 patients...") needs to be indented at the beginning.

- Table 5

  This table includes results for both the treatment-naïve and the cytokine-refractory studies. Please divide it into two separate tables instead. It is confusing to the reader to see the results for the cytokine-refractory studies before they are even discussed in the text.

- Figure 2

  Please delete the third decimal places from the hazard ratio and confidence interval within the table. Two places are sufficient and consistent with Figure 1's presentation.

- Please define the acronym "DR" upon first use in the label in this section.

15 References

- This entire section should be deleted from the label. Under the PLR, references should be included in the label only if they discuss an important recommendation by an authoritative scientific body, or a standardized methodology, scale, or technique. In general, literature references to clinical trials should not appear in labels.

16 How Supplied/Storage and Handling

- We recommend deleting the numbered subheadings from this section. Each dosage form does not need its own subheading.

17 Patient Counseling Information

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/s/

Iris Masucci
1/19/2007 12:54:18 PM
DDMAC REVIEWER

Laurie Burke
1/22/2007 06:43:05 PM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-938/S-004/S-005
NDA 21-968/S-005/S-006

PRIOR APPROVAL SUPPLEMENT

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Laurie M. Strawn, Ph.D.
Director, Worldwide Regulatory Strategy

Dear Dr. Strawn:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Sutent (sunitinib malate) Capsules 12.5 mg, 25 mg, 50 mg sunitinib equivalent
NDA Numbers:	21-938 and 21-968
Supplement numbers:	004/005 and 005/006, respectively
Review Priority Classification:	Priority (P)
Date of supplement:	August 9, 2006
Date of receipt:	August 9, 2006

These supplemental applications provide for revisions to the labeling based on final study reports from the following studies: "A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma" and "A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function". These study reports were submitted in fulfillment of post-marketing commitments from the January 26, 2006 approval of Sutent.

This application was filed on October 10, 2006, in accordance with 21 CFR 314.101(a). The user fee goal date is February 11, 2007.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the application numbers listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Consumer Safety Officer
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy Cottrell
1/19/2007 03:03:23 PM

Cottrell, Christy

From: Cottrell, Christy
Sent: Wednesday, January 31, 2007 12:02 PM
To: 'Strawn, Laurie'
Subject: Post-marketing commitments for SUTENT

Laurie,

We converted PMC #5 to a regular PMC as requested. In addition, for PMC #2 (fulfilled with this supplement), since the overall survival data and duration of response data are not mature, we need to make a new regular PMC for their submission.
See below.

1. Provide the complete study report and datasets with the final definitive statistical analysis of overall survival and duration of response for the study titled, "A Phase 3, Randomized Study of SU011248 versus Interferon-alpha as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma".

   Protocol Submission: submitted 6/2004
   Study Start: 8/2004
   Final Report Submission: TBD

Let me know if you agree with this PMC as written and please provide a date for final report submission.

One other thing....For PMC #9 (see below), the study report submission date is listed as 12/2006. Can you provide a new estimated date for submission of this report? (Note that it won't change the "delayed" status of the PMC, but it will give us an idea of when to expect it).

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".

   Protocol Submission: submitted 11/2003
   Study Start: 12/2003
   Final Report Submission: by 12/2006*

Thanks,
Christy

****

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

From: Cottrell, Christy
Sent: Wednesday, November 22, 2006 10:29 AM
To: 'Strawn, Laurie'; 'Mindy.Meader@pfizer.com'
Subject: NDA 21-968/S-005

Laurie/Mindy,

Please refer to your pending supplement NDA 21-968/S-005 for Sutent. See below for requests for additional information from the statistical and clinical pharmacology reviewers.

Statistical

1. Please tell us which datasets and variables (censoring indicator, time-to-event, and treatment) were used to produce the following tables in the CSR:

- Table 16, PFS analysis based on Core Radiology Assessment, ITT Population
- Table 19, TTP analysis based on Core Radiology Assessment, ITT Population
- Table 13.4.3.1.1 Overall Survival Analysis, ITT Population

2. The protocol indicated that the second interim analysis is for PFS analysis when approximately 354 events have occurred (approximately 75% of the total number of events expected). However, the actual number of PFS events for the interim analysis was 250. Please explain why the interim analysis was conducted after 250 events rather than after 354 as specified in the protocol.

Clinical Pharmacology

Request for data for study A6181079 (hepatic impairment study):

PK data:

- The PK dataset for sunitinib and its metabolite, by subject, is missing. Please submit datasets with individual concentration – time data as well as PK parameters for all subjects. Please also include individual protein binding data (Fu) for all subjects. Datasets should combine data from the control subjects as well as from the subjects that are hepatically-impaired.

Demographics and Laboratory values data:

- The demographics (demo.xpt), laboratory values (clchem.xpt), coagulation (clcoag.xpt) and vitals (vitals.xpt) datasets include data from only 14 of the 16 hepatically-impaired subjects and do not include data from the control group. Please re-submit the above datasets with data from all normal and hepatically-impaired subjects in the study.
- If possible, please submit a derived dataset to include the following variables from the above datasets: age, sex, race, height, weight, bilirubin, AST, ALT, albumin and PT, Child Pugh class, encephalopathy grade and ascites Grade.

Let me know if you have any questions.

Thanks,
Christy

****

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA

p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

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/s/

Christy Cottrell
11/22/2006 03:34:41 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-968/S-005

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
10646 Science Center Drive
San Diego, CA 92121

Attention: Laurie M. Strawn, Ph.D.
Director, Worldwide Regulatory Strategy

Dear Dr. Strawn:

Please refer to your August 9, 2006, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sutent (sunitinib malate) Capsules 12.5 mg, 25 mg, 50 mg sunitinib equivalent.

We also refer to your submissions dated August 16, September 29, October 10 and 13, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on October 10, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Labeling

Highlights

1. The Highlights section is too long. Please edit the contents of this section so it is no longer than half a page.

2. Please remove the ® symbol from the tradename immediately above the initial U.S. approval date.

3. Under Recent Major Changes, the heading, and if appropriate, subheading of the labeling section affected by the change, must be listed together. Therefore, it must read, "Indications and Usage, Advanced Renal Cell Carcinoma", not just "Indications and Usage". Please correct. In addition, the corresponding new or modified text under this section in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge.

4. Other than in the Recent Major Changes section, the corresponding sections of the FPI are not referenced anywhere else in Highlights. Please add these references.

5. Please remove the Pregnancy Category designation from the Warnings and Precautions section.

6. A summary of adrenal toxicity should be included under Warnings and Precautions.

7. The Adverse Reactions section should be updated to include only the most frequently occurring adverse reactions rather than all-causality adverse events.

8. The Adverse Reaction contact reporting statement in the Adverse Reactions section should be bolded.

Full Prescribing Information (FPI)

7. The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier [e.g., see *Indications and Usage (1.1)*]. Since cross-references are embedded in the text of the FPI, the use of italics to achieve emphasis is encouraged.

8. All identifying numbers must precede the heading or subheading by at least two square "ems" (i.e., two squares the size of the letter "m" in 8 point type).

9. In the Adverse Reactions section, you must include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials in which exposure occurred (e.g., placebo-controlled, active-controlled), and any critical exclusions from the safety database. Sample database description:

   "The data described below reflect exposure to drug X in [n] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo- and active-controlled trials (n=____, and n=____, respectively), and in long-term follow up studies. The population was [age range], [gender distribution], [race distribution], and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate]."

10. The Adverse Reactions section must also contain the standard statement: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice".

11. The Adverse Reactions section should contain only the controlled trial data, and should include only those events which occurred more frequently with Sutent than with placebo/IFN.

12. The Adverse Reactions section overview should contain a summary of frequent/important adverse reactions.

13. In the Use in Specific Populations section, the Hepatic Impairment subsection should be numbered 8.6 rather than 8.7. Please also revise the Contents section of the FPI to reflect this change.

14. In the Clinical Studies section, there are instances where the terms "primary" and "secondary" have been used to describe objectives. These should be removed.

15. In the Clinical Studies section, the demographics are presented in tabular format. Please delete the table and describe the demographics in text format indicating those criteria that are balanced or not. The demographic characteristics should generally be limited to the following: age, gender, race, performance status, disease characteristics (tumor type, stage), prior treatment, and predictors.

16. Please add a section 17.5 titled FDA-Approved Patient Labeling and attach the Patient Package Insert to the end of the FPI.

17. Manufacturer information should be located after the Patient Counseling Information section, at the end of the FPI. If the product will have FDA-approved patient labeling that is not a separate document or printed such that it is intended to be detached and distributed to patients, the manufacturer information should be located at the end of the labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit revised labeling in PLR SPL format to this NDA and to NDA 21-938 that addresses the deficiencies outlined above by November 17, 2006.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Christy Cottrell, Consumer Safety Officer at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Robert Justice
10/24/2006 05:38:42 PM

From: Cottrell, Christy
Sent: Wednesday, October 11, 2006 10:00 AM
To: 'Strawn, Laurie'
Subject: NDA 21-968/S-005

Laurie,

Please refer to your pending NDA 21-968/S-005 for Sutent. Below is a request for additional information from Dr. Goodman.

- It appears that you did not submit a complete set of the [redacted] datasets with this efficacy supplement. The current submission contains only a summary dataset but not the individual reader assessments of target, non-target and new lesions. Based on the original NDA submission, the data we do not have are the tables "[redacted]tlsn", "[redacted]ntlsn", "[redacted]nwlsn", "[redacted]tmpnt" and "[redacted]exam". Please submit these 5 datasets for the second interim analysis as soon as possible. b(4)

Let me know if you have any questions.

Thanks,
Christy

****

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

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/s/

Christy Cottrell
10/11/2006 10:17:47 AM
CSO

From: Cottrell, Christy
Sent: Thursday, October 05, 2006 1:37 PM
To: 'Strawn, Laurie'
Subject: NDA 21-968/S-005

Laurie,

Please refer to NDA 21-968/S-005 for Sutent. See below for an inquiry from the clinical reviewer:

Our review of progression-free survival events for the second interim analysis on study 6181034 has found 22 patients (11 per arm, as described in the tables below) who died prior to data cutoff on November 15, 2005 but who were censored for PFS in the interim analysis. Please explain why these deaths were not counted as events in the PFS analysis.

SUTENT

Patient ID	Date of death
A6181034-006476-00545	
A6181034-006476-00630	
A6181034-006652-00129	
A6181034-018748-00481	
A6181034-044602-00039	
A6181034-044602-00511	
A6181034-113571-00004	
A6181034-117102-00281	
A6181034-164789-00016	
A6181034-169936-00103	
A6181034-170369-00097	

b(6)

IFN-α

Patient ID	Date of death
A6181034-043999-00108	
A6181034-088279-00130	
A6181034-103636-00088	
A6181034-110114-00386	
A6181034-113571-00474	
A6181034-117102-00192	
A6181034-123453-00184	
A6181034-123453-00640	
A6181034-153668-00423	
A6181034-169936-00219	
A6181034-170353-00367	

b(6)

Please let me know if you have any questions.

Thanks,
Christy

****

Christy Cottrell

Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

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/s/

Christy Cottrell
10/5/2006 02:47:39 PM
CSO

From: Cottrell, Christy
Sent: Wednesday, October 04, 2006 3:06 PM
To: 'Strawn, Laurie'
Subject: NDA 21-968/S-005

Laurie,

Please refer to your pending supplemental NDA 21-968/S-005 for Sutent. See below for a request from the Study Endpoints and Label Development (SEALD) team that reviews SPL and PLR labeling:

- Please submit the completed Highlights Data Element Table. To complete the Highlights data elements, please refer to the following 2 documents at the FDA Data Standards Council website (http://www.fda.gov/oc/datacouncil) under Structured Product Labeling: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table". This table must be filled out with the terms that have been proposed for the Highlights data elements. The companion document provides information on the terminology to be used. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov.

Let me know if you have any questions.

Thanks,
Christy

****

Christy Cottrell
Consumer Safety Officer/Project Manager
Division of Drug Oncology Products, FDA
p: (301) 796-1347
f: (301) 796-9845
NEW EMAIL ADDRESS: christy.cottrell@fda.hhs.gov

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/s/

Christy Cottrell
10/4/2006 03:26:41 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-968 Supplement # 003 Efficacy Supplement Type SE-8

Trade Name: SUTENT
Established Name: sunitinib malate
Strengths: 12.5 mg, 25 mg, and 50 mg

Applicant: Pfizer Inc.
Agent for Applicant: Not Applicable

Date of Application: March 31, 2006
Date of Receipt: April 3, 2006
Date clock started after UN: Not Applicable
Date of Filing Meeting: May 30, 2006
Filing Date: June 3, 2006
Action Goal Date (optional): User Fee Goal Date: February 3, 2007

Indication(s) requested: Treatment of advance renal cell carcinoma

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☒ NO ☐

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☐ NO ☒

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance?
  N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☐ NO ☒

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☐

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☒

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 62,382

- End-of-Phase 2 Meeting(s)? Date(s) 11/10/03; 1/23/04; 2/23/05 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 9/23/04; 1/19/05; 4/19/05 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☐ NO ☒
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☐ NO ☒

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☒
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☒
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☒
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 30, 2006

BACKGROUND:

This supplemental application provided for fullfilment of post-marketing commitment items 1 and 3 as described in the approval letter dated January 26, 2006. This supplement includes the study report and datasets of the first interim efficacy and safety analysis for Study A6181034 entitled "A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma. This supplement includes the datasets containing the core imaging facility assessments used to derive the updated response rate for Study A6181006 entitled, "A Pivotal Study of SU011248 in the Treatment of Patients with Cytokine-Refractory Metastatic Renal Cell Carcinoma" (post-marketing commitment item 3).

On January 26, 2006, Sutent received accelerated approval for the treatment of advanced renal cell carcinoma and full approval for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

ATTENDEES: Robert Justice, M.D., Ann Farrell, M.D., Amna Ibrahim, M.D., Vicki Goodman, M.D., Ramzi Dagher, M.D., Rajeshwari Sridhara, Ph.D., Shenghui Tang, Ph.D., Patricia Garvey, R.Ph. for Christy Cottrell

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	**Reviewer**
Medical:	Vicki Goodman, M.D.
Secondary Medical:	----------
Statistical:	Shenghui Tang, Ph.D.
Pharmacology:	----------
Statistical Pharmacology:	----------
Chemistry:	----------
Environmental Assessment (if needed):	----------
Biopharmaceutical:	----------
Microbiology, sterility:	----------
Microbiology, clinical (for antimicrobial products only):	----------
DSI:	
Regulatory Project Management:	Patricia Garvey, R.Ph. for Christy Cottrell
Other Consults:	
DDMAC	Joseph Grillo, Pharm.D.

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY		FILE ☒	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments: Submitted in CTD format

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☐ Convey document filing issues/no filing issues to applicant by Day 74.
4. Send acknowledgment letter.

5. Send consult to DSI.

Patricia Garvey, R.Ph. for Christy Cottrell
Regulatory Project Manager, HFD-150

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/s/

Patricia Garvey
9/19/2006 12:43:53 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Interdisciplinary Review Team for QT Studies Attention: Devi Kazeli and/or Denise Hinton			HFD-150/Division of Drug Oncology Products Christy Cottrell, Consumer Safety Officer	
DATE August 7, 2006	IND NO.	NDA NO. NDA 21-938 NDA 21-968	TYPE OF DOCUMENT SLR-002 SLR-002	DATE OF DOCUMENT March 30, 2006
NAME OF DRUG Sutent (sunitinib malate) Capsules	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE September 15, 2006
NAME OF FIRM: Pfizer, Inc.				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

  Results of QT study

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

These labeling supplements include revised labeling based on the final study report for Study A6181005 titled, "A Phase 1 Study to Evaluate the Effects of SU011248 on QTc interval in Subjects with Advanced Solid Tumors" in response to a post-marketing commitment from the January 26, 2006 approval letter for NDAs 21-938 and 21-968. The Division requests feedback from the IRT by September 15, 2006. **This is an eCTD submission and is available in the EDR. DUE DATE: September 30, 2006**

MO: Vicki Goodman, MD
ClinPharm: Roshni Ramchandani, PhD
PM: Christy Cottrell (x61347)

	METHOD OF DELIVERY (Check one) X MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Christy Cottrell
8/7/2006 01:13:59 PM
DR: Please process this outgoing consult. The submission is available in the EDR.

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in IMTS for this cancellation.

Complete the information below and check form into DFS.

Application Type	☐ P-IND X IND ☐ NDA
Application Number	IND 62,382
DATE Meeting Cancelled (per communication with requester)	June 27, 2006
Scheduled Meeting Date	June 29, 2006
Reason for Cancellation	Draft responses were sent to Pfizer on June 26, 2006 (attached). After reviewing the responses, Pfizer determined that no further discussion was needed and cancelled the meeting.
Project Manager	Christy Cottrell

Establishment of Clinical Benefit and Traditional Approval

1. Study A6181034 is a randomized, multi-center, international Phase 3 clinical trial with 1:1 randomization evaluating the efficacy and safety of single-agent sunitinib compared to IFN-α as a first-line therapy in patients with metastatic RCC. It was designed to verify the clinical benefit of sunitinib in RCC. The study has met its primary objective to compare the PFS associated with sunitinib versus that associated with IFN-α. The efficacy data submitted will include PFS, ORR, duration of response and OS. In addition to the efficacy data, this submission will include safety data from Study A6181034 and a cumulative Safety Update as described in Section 3.3. Pfizer expects that the proposed submission will verify the clinical benefit and support the conversion of the advanced RCC indication from accelerated to traditional approval.

   Given that Study A6181034 has met its primary objective to demonstrate a PFS advantage for sunitinib over IFN-α and the safety data demonstrate appropriate safety, does the FDA agree that this submission will provide the substantial evidence of clinical benefit required for the conversion of NDA 21-968 from accelerated approval to traditional approval?

   FDA RESPONSE:

   - If review of the submission demonstrates that the improvement in PFS for the sunitinib arm is clinically and statistically significant, and demonstrates that the benefits of sunitinib therapy outweigh the safety risks, then this submission will be sufficient to satisfy the subpart H requirement to demonstrate clinical benefit.

LVEF Assessments in Adjuvant RCC Study

2. As discussed in a Pfizer/FDA teleconference held on 05 January 2006, submission of LVEF data from the NCI/ECOG-sponsored study, E2805 titled "A Randomized, Double- Blind Phase III Trial of Adjuvant Sunitinib Versus Sorafenib Versus Placebo in Patients with Resected Renal Cell Carcinoma" would be a Subpart H post-marketing commitment. At a subsequent teleconference held on 23 January 2006, Pfizer pointed out that a final clinical study report for this blinded study would not be available until at least 2011. The FDA agreed to add a statement to post-marketing commitment 5 that the protocol will be revised to include a plan for LVEF monitoring that is acceptable to the FDA. Pfizer's understanding is that submission of this revised protocol by NCI will meet the Subpart H post-marketing commitment. The specific details of the plan for LVEF assessments were further discussed in a teleconference held on 28 March 2006. A Statistical Analysis Plan for reviewing LVEF data at interim time points was submitted to NDA 21-968 on 18 April 2006, and NCI/ECOG is currently in the process of amending the protocol to add additional LVEF assessments. We propose that the post-marketing commitment to submit the final LVEF data, due in 2011, be changed to a regular, non-Subpart H post-marketing commitment.

Does the FDA agree that:

a. submission of the revised Protocol E2805, including an acceptable LVEF monitoring plan, is adequate to meet the Subpart H post-marketing commitment?

FDA RESPONSE:

- No. However, we are willing to convert the Subpart H post-marketing commitment to a regular post-marketing commitment.

b. submission of the final LVEF data from the adjuvant RCC study can be considered a regular post-marketing commitment?

FDA RESPONSE:

- Yes. However, since the data should be available prior to 2011, please revise your timeline for submission.

Study Reports and Summaries

3. This supplement will provide an updated label in the SPL format including the PFS data from the study in treatment-naïve RCC patients (Study A6181034), the Clinical Study Report for the confirmatory Phase 3 Study A6181034, a Clinical Overview, and a Safety Update. Pfizer will not provide a revised SCE. The SCPS and SBS will not be updated since at this point there are no new significant clinical pharmacology or biopharmaceutic data available. Furthermore, there are no new non-clinical or quality data available, so the supplement will not include Module 3 or 4 documents.

   Does the agency agree with the above approach regarding the application content and with the documents to be included in this supplement?

   FDA RESPONSE:

   - Yes.

Safety Narratives

4. As discussed in Section 3.4.1, Pfizer plans to prepare narratives for patients who experienced treatment-related SAEs, died of causes not associated with disease progression or discontinued because of treatment-emergent, all-causality SAEs. Due to the large number of patients on ongoing sunitinib clinical studies to be included in SU2, approximately 500 patients meet these criteria. It is possible that not all of the narratives will be completed at the planned time of this submission. Thus, in the event that all narratives are not completed by July, we propose to submit narratives for patients who died or discontinued because of SAEs with this submission, and to submit narratives for patients who experienced treatment-related SAEs in a subsequent submission.

   Is it acceptable to the FDA to submit narratives for patients who experienced treatment-related SAEs in a subsequent submission if they are not available in July?

   FDA RESPONSE:

   - Please provide a proposed timeline for the submission of these narratives.

Exposure/Efficacy Analysis

5. [redacted] b(4)

. Pfizer is currently analyzing the samples and constructing the datasets in order to perform the analysis exploring relationships between exposure and efficacy outcomes from Study A6181034. Pfizer will supply a report within 2 months after this submission.

Does the agency agree with the above approach to provide the PK/PD report at a later date, as it is not part of the Subpart H commitments?

FDA RESPONSE:

- Yes.

Core Radiology Imaging System

6. [redacted] has provided the independent third-party review of tumor assessments (computed tomography or magnetic resonance imaging scans) for pivotal Study A6181034. Pfizer is proposing not to submit the scans and spreadsheets from [redacted] but to make them available upon request. Raw and derived datasets from the [redacted] analyses will be included in this submission. b(4)

Does the agency agree with this approach of making the scans and spreadsheets from [redacted] available upon request instead of supplying them with this submission?

FDA RESPONSE:

- Yes.

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/s/

Christy Cottrell
7/14/2006 11:28:43 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-968/S-003

PRIOR APPROVAL SUPPLEMENT

Pfizer, Inc.
Attention: Laurie M. Strawn, Ph.D.
Associate Director, Worldwide Regulatory Strategy
10777 Science Center Drive
San Diego, CA 92121

Dear Dr. Strawn:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	SUTENT (sunitinib malate) Capsules
NDA Number:	21-968
Supplement number:	003
Review Priority Classification:	Standard (S)
Date of supplement:	March 31, 2006
Date of receipt:	April 3, 2006

This supplemental application includes the study report of the first interim efficacy and safety analysis for Study A6181034 entitled "A Phase 3, Randomized Study of SU011248 versus Interferon-α as First-Line Systemic Therapy for Patients with Metastatic Renal Cell Carcinoma". This report and the datasets meets post-marketing commitment item 1 as described in the approval letter issued on January 26, 2006.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 2, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 3, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Patricia N. Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Patricia Garvey
6/1/2006 12:35:11 PM

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Friday, April 28, 2006 11:27 AM
To: 'laurie.strawn@pfizer.com'
Subject: Sutent meeting request

In response to your April 21, 2006 request for a pre-IND meeting re: Sutent, we have a tentative date of Thurs., June 29, 2006 at 1:30 at our new FDA **White Oak Campus**, 10903 New Hampshire Ave., Building 22, Silver Spring, MD 20993. If this date is acceptable, we will need 15 copies of the package, with your questions included (please provide questions by E-Mail or diskette also), by June 1. We usually conduct our meetings to center around your questions, i.e., we don't generally have presentations since all the needed information has been presented in your preparation package. Also, I will fax you our draft responses to your questions after our internal pre-meeting (June 22) ; you can then decide if a face-to-face meeting with us is still necessary. If we have a meeting, I will have your questions and our responses on the overheads for discussion/revision. They will serve as the basis for the FDA official minutes of the meeting. Let me know your response ASAP. I have attached the list of FDA invitees for the meeting.

Richard Pazdur, M.D., Dir., OODP (invited)
Karen Weiss, M.D., Dep. Dir., OODP (invited)
Robert Justice, M.D., Acting Dir., DDOP
Ann Farrell, M.D., Acting Dep. Dir., DDOP
Amna Ibrahim, M.D., Acting Medical Team Leader, DDOP
Vicki Goodman, M.D., Medical Officer, DDOP
Raji Sridhara, Ph.D., Stat. Team Leader
Shenghui Tang, Ph.D., Statistician
Eric Duffy, Ph.D., Dir., Div. Post-Marketing Assess., ONDQA (invited)
Hasmukh Patel, Ph.D., Branch Chief, Branch VIII, ONDQA (invited)
Liang Zhou, Ph.D., Chemistry PAL, Branch VIII, ONDQA (invited)
David Morse, Ph.D., Pharm. Team Leader, DDOP (invited)
Leigh Verbois, Ph.D., Pharmacologist, DDOP (invited)
Brian Booth, Ph.D., Acting Clin. Pharm. and Bioph. TL, OCPB (invited)
Roshni Ramchandani, Ph.D., Clin. Pharm./Bioph. Rev., OCPB (invited)
Dotti Pease, Project Manager, DDOP
Christy Cottrell, Project Manager, DDOP

Thanks

Dotti for Christy
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
301 796-1434 fax 301 796-9845

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/s/

Dotti Pease
4/28/2006 01:12:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

NDA 21-968

Pfizer Inc.
Attention: Laurie M. Strawn, Ph.D.
Associate Director, Worldwide Regulatory Strategy
10777 Science Center Drive, Bldg. 85
San Diego, CA 92121

Dear Dr. Strawn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sutent (sunitinib malate) Capsules.

We also refer to the teleconference between you and the FDA on March 28, 2006. The purpose of this teleconference was to reach agreement with the Agency on the planned LVEF assessments in this study.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions me at (301)796-1356.

Sincerely,

{See appended electronic signature page}

Patricia N. Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

TELECONFERENCE MINUTES

MEETING DATE: March 28, 2006 **TIME:** 11:00 am

NDA 21-968 **Meeting Request Submission Date:** 3-9-06

DRUG: Sutent (sunitinib malate) Capsules

SPONSOR/APPLICANT: Pfizer Inc.

TYPE OF MEETING:

1. Guidance (Type A meeting)

2. **Proposed Indication:** Adjuvant renal cell carcinoma (RCC)

FDA PARTICIPANTS:

Robert Justice, M.D.	--	Acting Director, Division Drug Oncology Products (Chair)
John Johnson, M.D.	--	Medical Team Leader
Vicki Goodman, M.D.	--	Medical Reviewer
Robert White, M.D.	--	Medical Reviewer
Robert Kane, M.D.	--	Medical Reviewer
Shenghui Tang, Ph.D.	--	Statistical Reviewer, Division of Biostatistics V (DBV)
Patty Garvey, R.Ph.	--	Senior Regulatory Project Manager (Facilitator)

Pre-meeting:	Richard Pazdur,M.D.	--	Director, Office of Oncology Drug Products
	Mark Rothmann,PhD	--	Statistical Team Leader, DBV
	Paul Zimmerman	--	Senior Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Chuck Baum, M.D.	--	Executive Director, Oncology Clinical Research
Samuel Dychter, M.D.	--	Director, Safety Risk Management
Subramanian Hariharan, M.D.	--	Medical Director, US Medical
Sakina Hoosen, M.D.	--	Medical Director/Team Leader, US Medical
Randy Allred, Ph.D.	--	Senior Director, Biostatistics
Rana Fayyad, Ph.D.	--	Associate Director, Biostatistics
Laurie Strawn, Ph.D.	--	Associate Director, Regulatory Affairs
Ann Carey	--	Director, Regulatory Affairs
Carl DeJuliis, Ph.D.	--	Associate Director, Regulatory Affairs

MEETING OBJECTIVE:

To reach agreement on the planned left ventricular ejection fraction (LVEF) assessments in the study of sunitinib for adjuvant RCC treatment as required by postmarketing study commitment 5.

BACKGROUND:

Sunitinib is a small molecule, multi-targeted tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinases (RTKs) involved in the tumor cell growth and angiogenesis.

On January 26, 2006, sunitinib as received full approval for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and accelerated approval for advanced renal cell carcinoma (RCC).

As of February 22, 2006, over 4000 cancer patients and 158 healthy volunteers have been enrolled in Phase 1, 2 and 3 clinical studies investigating the pharmacokinetics, safety, and efficacy of sunitinib. In addition to the efficacy demonstrated in the pivotal and supportive studies in patients with GIST and RCC, clinical activity has been observed in Phase 2 studies of patients with breast cancer, non-small cell lung cancer, and neuroendocrine tumor. A pivotal Phase 3 study of sunitinib versus interferon-alpha in patients with treatment-naïve RCC is closed to enrollment, but treatment is ongoing. In addition, a placebo-controlled study of adjuvant treatment of RCC patients with sunitinib is planned in collaboration with the National Cancer Institute (NCI). As a post-marketing commitment for sunitinib, left ventricular ejection fraction (LVEF) assessments are to be included in this study.

The purpose of this meeting is to reach agreement on the planned LVED assessments in the study of sunitinib for adjuvant RCC treatment.

QUESTIONS for DISCUSSION AND FDA RESPONSES:

NOTE: FDA sent the sponsor draft FDA responses to the meeting on March 22, 2006.

1. Timing of Study Initiation: Is it acceptable to initiate Study E2805 for the adjuvant treatment of RCC patients prior to amending the protocol to include LVEF assessments?

   FDA Response:

   No. As discussed between DDOP and NCI on February 8, 2006, an amendment to require baseline and 3-month LVEF measurements in all patients should be enacted prior to initiating the trial. The trial will subsequently be amended within approximately 1 month of initiation to include MUGA scans at 6 and 12 months and off-study or for cause.

   It is not clear why an amendment encompassing all MUGA scans (a baseline, 3 months, 6 months, 12 months or end of treatment, and for cause) can not be submitted at this time to IRB as amendment. Please provide us with a written rationale for a two-step process.

Discussion:

Pfizer provided an update on the current status of the protocol. Pfizer reiterated that the NCI would be the sponsor of the study, and holds the IND. The initial protocol, E2805 was written by Dr. Naomi Haas (Principal Investigator, ECOG) on November 28, 2005. The protocol was reviewed by NCI /CIRB on December 19, 2005 and further comments from NCI were sent to ECOG on January 6, 2006.

In January and February, 2006 Pfizer discussed FDA's comments regarding LVEF monitoring in protocol E2805 with the NCI and ECOG, and held a formal meeting on March 2, 2006. The NCI and FDA also discussed the LVEF monitoring for study E2805 on February 8, 2006. Based on these discussions, ECOG revised the protocol. This was again reviewed by NCI/CTEP review on February 15, 2006.

The current final version of the protocol was submitted by ECOG on February 28, 2006. This includes a baseline MUGA scan and a 3-month MUGA scan on all patients enrolled in the E2805 study. This version of the protocol was approved by CIRB on March 24, 2006. It is awaiting final approval by the NCI for activation of the study. The current protocol will be amended to include MUGA assessments at 6 months, 12 months, and also end of treatment MUGA scan for patients who withdraw during the 12-month treatment period. If an abnormal MUGA scan result is seen at 12 months, the patient will be assessed by repeat MUGA scans at approximately 3-month intervals until the LVEF is within the normal range.

The FDA agreed with the proposed changes to the monitoring. FDA stated that a MUGA should be performed at the time of study discontinuation if the patient withdraws prematurely. Pfizer will request that the NCI/ECOG amend the protocol to include the additional LVEF assessments. Pfizer will notify the FDA when this amendment is submitted.

2. Sample Size: Does the Agency agree that a subset of 255 patients (85 per arm) is sufficient to evaluate LVEF in this study of 1332 patients?

FDA Response:

The evaluation of LVEF should initially be performed in all treated patients. You may submit a proposal to discontinue routine LVEF monitoring if clinically and statistically persuasive data in the initial cohort of patients suggest no significant increase in cardiac risk for patients receiving Sutent.

Comparison of absolute difference in LVEF between groups is not acceptable. We are interesting in comparing the proportions of patients between Sutent and placebo treatment arms experiencing cardiac toxicities based on a predefined reduction in LVEF (this may be similar in your phase 3 GIST trial).

Pfizer Response:

Based on the above FDA Response, Pfizer submitted by e-mail on March 27, 2006 the following for discussion at the scheduled teleconference:

> With regard to the Agency's response to Question 2, we acknowledge that you are interested in analyzing the proportion of patients with an event. The data in the label for the GIST Phase 3 study are for declines to below the lower limit of normal (LLN) without taking into account that some of the changes may have been very small and are probably not clinically relevant. We would like to discuss using a criteria of a decline of at least 10% to below the LLN so that patients with a very small, non-clinically significant decline are not included in the results.

Discussion:

FDA accepted the proposed event definition of a drop in LVEF below LLN (50%) and an absolute decrease of 10% from baseline.

Pfizer discussed the statistical plan for interim analyses to determine if LVEF assessments may be stopped based on no differences between arms. Pfizer proposed 2 interim analyses: the first one after 1/3 of subjects (approx. 148 subjects per arm) have had their 6-month MUGA scans, and the second after 2/3 of subjects (296 subjects per arm) have completed 6-month MUGA scans. To decide whether to stop LVEF assessments in the study, Pfizer is recommending using the Gamma (-2) futility stopping boundaries, which are more conservative than Pocock boundaries, and less conservative than O'Brien Fleming (OF) boundaries in terms of stopping early. The interim results of the LVEF analysis will be presented to the ECOG Data Monitoring Committee (DMC) by blinded treatment groups. Based on the futility boundaries specified, if there is no difference between treatment arms A and B, A and C, and B and C, the protocol will be amended to stop LVEF assessments on all subjects by MUGA scans. If there are differences between any of the treatment arms, the DMC may request to review the unblinded data. A written plan for what will be done based on the various possible outcomes will be in place prior to the analysis.

Before the Agency can comment on the acceptability of this plan, the FDA requested that statistical analysis plan (SAP) be submitted for review. Pfizer agreed to submit the SAP.

3. Cardiac Monitoring: Does the agency agree with the use of MUGA scans for LVEF assessments to be conducted at a subset of approximately 30 clinical sites on the proposed schedule?

FDA Response: No, Please see above.

Discussion:

Pfizer requested clarification on whether MUGA scan were acceptable in order to measure LVEF. The FDA stated that MUGA scans are acceptable.

ACTION ITEMS:

1. Pfizer will notify FDA when the NCI/ECOG protocol amendment to include the additional LVEF assessments is submitted.

2. Pfizer will submit a statistical analysis plan for their 2 proposed interim analyses.

There were no unresolved issues. The meeting concluded at 11:30 am

{See appended electronic signature page}

Patty Garvey, R.Ph.
Senior Regulatory Project Manager/Facilitator

{See appended electronic signature page}

Concurrence Chair:

Robert Justice, M.D.
Acting Director, DDOP

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/s/

Robert Justice
4/13/2006 05:51:24 PM

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/s/

Patricia Garvey
4/17/2006 01:04:13 PM

TELECONFERENCE MINUTES

MEETING DATE: March 28, 2006 **TIME:** 11:00 am

NDA 21-968 **Meeting Request Submission Date:** 3-9-06

DRUG: Sutent (sunitinib malate) Capsules

SPONSOR/APPLICANT: Pfizer Inc.

TYPE OF MEETING:

1. Guidance (Type A meeting)

2. **Proposed Indication:** Adjuvant renal cell carcinoma (RCC)

FDA PARTICIPANTS:

Robert Justice, M.D.	--	Acting Director, Division Drug Oncology Products (Chair)
John Johnson, M.D.	--	Medical Team Leader
Vicki Goodman, M.D.	--	Medical Reviewer
Robert White, M.D.	--	Medical Reviewer
Robert Kane, M.D.	--	Medical Reviewer
Shenghui Tang, Ph.D.	--	Statistical Reviewer, Division of Biostatistics V (DBV)
Patty Garvey, R.Ph.	--	Senior Regulatory Project Manager (Facilitator)

Pre-meeting:	Richard Pazdur,M.D.	--	Director, Office of Oncology Drug Products
	Mark Rothmann,PhD	--	Statistical Team Leader, DBV
	Paul Zimmerman	--	Senior Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Chuck Baum, M.D.	--	Executive Director, Oncology Clinical Research
Samuel Dychter, M.D.	--	Director, Safety Risk Management
Subramanian Hariharan, M.D.	--	Medical Director, US Medical
Sakina Hoosen, M.D.	--	Medical Director/Team Leader, US Medical
Randy Allred, Ph.D.	--	Senior Director, Biostatistics
Rana Fayyad, Ph.D.	--	Associate Director, Biostatistics
Laurie Strawn, Ph.D.	--	Associate Director, Regulatory Affairs
Ann Carey	--	Director, Regulatory Affairs
Carl DeJuliis, Ph.D.	--	Associate Director, Regulatory Affairs

MEETING OBJECTIVE:

To reach agreement on the planned left ventricular ejection fraction (LVEF) assessments in the study of sunitinib for adjuvant RCC treatment as required by postmarketing study commitment 5.

BACKGROUND:

Sunitinib is a small molecule, multi-targeted tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinases (RTKs) involved in the tumor cell growth and angiogenesis.

On January 26, 2006, sunitinib as received full approval for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and accelerated approval for advanced renal cell carcinoma (RCC).

As of February 22, 2006, over 4000 cancer patients and 158 healthy volunteers have been enrolled in Phase 1, 2 and 3 clinical studies investigating the pharmacokinetics, safety, and efficacy of sunitinib. In addition to the efficacy demonstrated in the pivotal and supportive studies in patients with GIST and RCC, clinical activity has been observed in Phase 2 studies of patients with breast cancer, non-small cell lung cancer, and neuroendocrine tumor. A pivotal Phase 3 study of sunitinib versus interferon-alpha in patients with treatment-naïve RCC is closed to enrollment, but treatment is ongoing. In addition, a placebo-controlled study of adjuvant treatment of RCC patients with sunitinib is planned in collaboration with the National Cancer Institute (NCI). As a post-marketing commitment for sunitinib, left ventricular ejection fraction (LVEF) assessments are to be included in this study.

The purpose of this meeting is to reach agreement on the planned LVED assessments in the study of sunitinib for adjuvant RCC treatment.

QUESTIONS for DISCUSSION AND FDA RESPONSES:

NOTE: FDA sent the sponsor draft FDA responses to the meeting on March 22, 2006.

1. Timing of Study Initiation: Is it acceptable to initiate Study E2805 for the adjuvant treatment of RCC patients prior to amending the protocol to include LVEF assessments?

   FDA Response:

   No. As discussed between DDOP and NCI on February 8, 2006, an amendment to require baseline and 3-month LVEF measurements in all patients should be enacted prior to initiating the trial. The trial will subsequently be amended within approximately 1 month of initiation to include MUGA scans at 6 and 12 months and off-study or for cause.

   It is not clear why an amendment encompassing all MUGA scans (a baseline, 3 months, 6 months, 12 months or end of treatment, and for cause) can not be submitted at this time to IRB as amendment. Please provide us with a written rationale for a two-step process.

Discussion:

Pfizer provided an update on the current status of the protocol. Pfizer reiterated that the NCI would be the sponsor of the study, and holds the IND. The initial protocol, E2805 was written by Dr. Naomi Haas (Principal Investigator, ECOG) on November 28, 2005. The protocol was reviewed by NCI /CIRB on December 19, 2005 and further comments from NCI were sent to ECOG on January 6, 2006.

In January and February, 2006 Pfizer discussed FDA's comments regarding LVEF monitoring in protocol E2805 with the NCI and ECOG, and held a formal meeting on March 2, 2006. The NCI and FDA also discussed the LVEF monitoring for study E2805 on February 8, 2006. Based on these discussions, ECOG revised the protocol. This was again reviewed by NCI/CTEP review on February 15, 2006.

The current final version of the protocol was submitted by ECOG on February 28, 2006. This includes a baseline MUGA scan and a 3-month MUGA scan on all patients enrolled in the E2805 study. This version of the protocol was approved by CIRB on March 24, 2006. It is awaiting final approval by the NCI for activation of the study. The current protocol will be amended to include MUGA assessments at 6 months, 12 months, and also end of treatment MUGA scan for patients who withdraw during the 12-month treatment period. If an abnormal MUGA scan result is seen at 12 months, the patient will be assessed by repeat MUGA scans at approximately 3-month intervals until the LVEF is within the normal range.

The FDA agreed with the proposed changes to the monitoring. FDA stated that a MUGA should be performed at the time of study discontinuation if the patient withdraws prematurely. Pfizer will request that the NCI/ECOG amend the protocol to include the additional LVEF assessments. Pfizer will notify the FDA when this amendment is submitted.

2. Sample Size: Does the Agency agree that a subset of 255 patients (85 per arm) is sufficient to evaluate LVEF in this study of 1332 patients?

FDA Response:

The evaluation of LVEF should initially be performed in all treated patients. You may submit a proposal to discontinue routine LVEF monitoring if clinically and statistically persuasive data in the initial cohort of patients suggest no significant increase in cardiac risk for patients receiving Sutent.

Comparison of absolute difference in LVEF between groups is not acceptable. We are interesting in comparing the proportions of patients between Sutent and placebo treatment arms experiencing cardiac toxicities based on a predefined reduction in LVEF (this may be similar in your phase 3 GIST trial).

Pfizer Response:

Based on the above FDA Response, Pfizer submitted by e-mail on March 27, 2006 the following for discussion at the scheduled teleconference:

> With regard to the Agency's response to Question 2, we acknowledge that you are interested in analyzing the proportion of patients with an event. The data in the label for the GIST Phase 3 study are for declines to below the lower limit of normal (LLN) without taking into account that some of the changes may have been very small and are probably not clinically relevant. We would like to discuss using a criteria of a decline of at least 10% to below the LLN so that patients with a very small, non-clinically significant decline are not included in the results.

Discussion:

FDA accepted the proposed event definition of a drop in LVEF below LLN (50%) and an absolute decrease of 10% from baseline.

Pfizer discussed the statistical plan for interim analyses to determine if LVEF assessments may be stopped based on no differences between arms. Pfizer proposed 2 interim analyses: the first one after 1/3 of subjects (approx. 148 subjects per arm) have had their 6-month MUGA scans, and the second after 2/3 of subjects (296 subjects per arm) have completed 6-month MUGA scans. To decide whether to stop LVEF assessments in the study, Pfizer is recommending using the Gamma (-2) futility stopping boundaries, which are more conservative than Pocock boundaries, and less conservative than O'Brien Fleming (OF) boundaries in terms of stopping early. The interim results of the LVEF analysis will be presented to the ECOG Data Monitoring Committee (DMC) by blinded treatment groups. Based on the futility boundaries specified, if there is no difference between treatment arms A and B, A and C, and B and C, the protocol will be amended to stop LVEF assessments on all subjects by MUGA scans. If there are differences between any of the treatment arms, the DMC may request to review the unblinded data. A written plan for what will be done based on the various possible outcomes will be in place prior to the analysis.

Before the Agency can comment on the acceptability of this plan, the FDA requested that statistical analysis plan (SAP) be submitted for review. Pfizer agreed to submit the SAP.

3. Cardiac Monitoring: Does the agency agree with the use of MUGA scans for LVEF assessments to be conducted at a subset of approximately 30 clinical sites on the proposed schedule?

FDA Response: No, Please see above.

Discussion:

Pfizer requested clarification on whether MUGA scan were acceptable in order to measure LVEF. The FDA stated that MUGA scans are acceptable.

ACTION ITEMS:

1. Pfizer will notify FDA when the NCI/ECOG protocol amendment to include the additional LVEF assessments is submitted.

2. Pfizer will submit a statistical analysis plan for their 2 proposed interim analyses.

There were no unresolved issues. The meeting concluded at 11:30 am

{See appended electronic signature page}

Patty Garvey, R.Ph.
Senior Regulatory Project Manager/Facilitator

{See appended electronic signature page}

Concurrence Chair:
Robert Justice, M.D.
Acting Director, DDOP

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/s/

Robert Justice
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FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road, Beltsville, MD 20705-1266
10903 New Hampshire Avenue, Building #22, Silver Spring, MD 20993

To: Laurie Strawn, Ph.D.	**From:** Christy Cottrell
Fax: (858) 678-8163	**Fax:** (301) 796-9867
Phone: (858) 518-4890	**Phone:** (301) 796-1347
Pages, including cover sheet: 2	**Date:** 3-14-06

Re: NDA 21-968 for Sutent: Type A meeting confirmation

Laurie,

This fax serves to confirm the scheduling of a Type A meeting to reach agreement on the planned LVEF assessments in the study of sunitinib for adjuvant RCC.

DATE: March 28, 2006 **TIME:** 11:00 am EST

LOCATION: Federal Research Campus at White Oak
10903 New Hampshire Avenue, Building #22
Silver Spring, Maryland

FDA PARTICIPANTS:

Robert Justice, M.D., Acting Director
Acting Deputy Director
Vicki Goodman, M.D., Clinical Reviewer
Shenghui Tang, Ph.D. Statistical Reviewer
Mark Rothmann, Ph.D., Acting Statistical Team Leader
John Johnson, M.D., Clinical Team Leader
Robert White, Jr., M.D., Clinical Reviewer
David Morse, Ph.D., Pharm/Tox Team Leader
Patty Garvey, Consumer Safety Officer (for Christy Cottrell)

The following individuals have been invited to the meeting, but may not attend:

Robert Kane, M.D., Clinical Reviewer
Edwin Rock, M.D., Clinical Reviewer
Amna Ibrahim, M.D., Acting Clinical Team Leader
Karen Weiss, M.D., Deputy Office Director
Richard Pazdur, M.D., Office Director
Paul Zimmerman, Consumer Safety Officer

We note that the background packages for this meeting have already been submitted.

If you have any questions, feel free to call me at (301) 796-1347 or Patty Garvey at (301) 796-1356.

Thanks,

Christy Cottrell

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/s/

Christy Cottrell
3/14/2006 10:37:21 AM