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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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

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 V
OND Division:	Division of Drug Oncology Products (HFD-150)
Submission Dates:	10-Aug-2005, 14-Oct-2005, 22-Dec-2005, 10-Jan-2005
OCPB Reviewers:	Roshni Ramchandani, Ph.D. Sophia Abraham, Ph.D. Carol Noory, Ph.D.
Pharmacometrics Reviewer:	Roshni Ramchandani, Ph.D.
OCPB Team Leader:	Brian Booth, Ph.D.
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Type of Submission:	NDA-NME

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1. EXECUTIVE SUMMARY

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). The proposed indications for sunitinib are: 1) treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate, and 2) treatment of advanced renal cell carcinoma.

The applicant has conducted several phase 1 studies in healthy volunteers and patients with solid tumors and acute myelogenous leukemia (AML) to evaluate safety and pharmacokinetics (PK) of sunitinib and its primary active metabolite SU012662. Sunitinib was orally available, with a slow rate of absorption and a high apparent volume of distribution. The primary pathway of elimination of sunitinib is via CYP3A4 mediated metabolism to the active primary metabolite SU012662. Both sunitinib and SU012662 are eliminated in the feces with renal elimination accounting for 16% of the administered dose. Drug-drug interaction studies have shown a 51% increase in combined (sunitinib+SU012662) exposure when co-administered with ketoconazole and a 46% reduction in combined (sunitinib+SU012662) exposure when co-administered with rifampin.

The applicant has also conducted two studies in gastrointestinal stromal tumor (GIST) patients, a single arm study and a placebo-controlled study, and 2 single-arm studies in metastatic renal cell carcinoma (MRCC) patients to evaluate the effectiveness and toxicity of sunitinib. The GIST and MRCC studies included trough PK data collection for evaluation of exposure-response relationships. GIST patients showed a significantly lower time to tumor progression (primary end point for GIST) on sunitinib compared to placebo. MRCC patients showed objective response rates for partial responses (primary end point for MRCC) of 26.5% and 36.5% in the two single-arm studies. Median duration of response in MRCC patients was 27.1 and 54 weeks in the two studies. Exposure-response analysis of effectiveness measures indicated significant relationships for time to tumor progression with exposure in GIST patients. Increases in AUC were found to be associated with a lower risk of progression. Additional analysis showed that increases in AUC were associated with lower minimum absolute tumor sizes in GIST patients. No significant relationships were seen for response rates or time to tumor progression in MRCC patients.

The major toxicities associated with sunitinib included severe fatigue, diarrhea, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction (LVEF) dysfunction. Most of these adverse events were found to be exposure-related. An increase in exposure was associated with an increased incidence of fatigue, thrombocytopenia, anemia, neutropenia, hypertension and LVEF dysfunction.

1.1. Recommendations

Recommendations to the sponsor

A. Dosing adjustments for patients on CYP3A4 inhibitors
There was an approximately 51% increase in combined AUC of sunitinib and active metabolite when sunitinib was concomitantly given with ketoconazole. To adjust for this increase, we recommend that the sunitinib dose be reduced to a minimum of 37.5 mg in patients receiving strong CYP3A4 inhibitors.

B. Dosing adjustments for patients on CYP3A4 inducers
There was an approximately 46% decrease in combined AUC of sunitinib and active metabolite when sunitinib was concomitantly given with rifampin. To adjust for this decrease, we recommended that the sunitinib dose be increased in 12.5 mg increments to a maximum of 87.5 mg in patients receiving CYP3A4 inducers.

C. Dissolution method specifications:
Data provided during method development and stability testing and indicates that the tolerance specification proposed by the applicant (Q=[ ]% at 30 minutes) may not be sufficiently robust. A tolerance specification of Q=[ ] at 30 minutes is more appropriate for this product. The final recommended dissolution procedure and specification are:

Apparatus:	USP Apparatus II (Paddle Method)
Rotation Speed:	rpm
Medium:	0.1M HCl
Volume:	900 mL
Analytical:	UV Spectroscopy
Tolerance:	Q= [ ] at 30 minutes

D. Biowaiver for 25 mg capsule granted:

The Agency requested dissolution data for the 25 mg capsule from the sponsor. A waiver of the *in vivo* bioequivalence data necessary for the approval of the 25-mg strength sunitinib malate capsule was granted based on linear comparable composition across the strengths to-be-marketed, the high solubility across the pH range of pH 1.2 to pH 6.8, and the in vitro dissolution comparison of the profiles generated for three 25-mg commercial batches and the 50-mg clinical trial batch.

Labeling Recommendations

Please refer to Detailed Labeling Recommendations on page 65.

1.2. Phase IV Commitments

A. QTc prolongation study:
Submit completed study report for ongoing QTc prolongation study titled: "A Phase I Study to Evaluate the Effect of SU011248 on QTc Interval in Subjects with Advanced Solid Tumors. (A6181005)"

B. Hepatic impairment study:
Submit completed study report for ongoing hepatic impairment study titled "A Phase 1 Study to Evaluate the Pharmacokinetics of SU011248 in Subjects with Impaired Hepatic Function".

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Sunitinib malate is manufactured as an immediate release hard gelatin capsule representing doses of 12.5 mg, 25 mg and 50 mg of SU011248 as sunitinib malate. The 12.5 mg capsule uses a blend formula containing — w/w of sunitinib malate, whereas the 25 mg and 50 mg capsules use a blend formula containing — w/w sunitinib malate. To support the biopharmaceutics portion of the application, the sponsor conducted two exploratory studies and three bioavailability studies to evaluate the safety, tolerability, pharmacokinetics and the effect of food on sunitinib free base and malate salt. These studies were also used to establish the bioequivalence of the 50 mg and the 12.5 mg commercial products to the clinical trial formulations. In vitro bioequivalence was established for the 25 mg sunitinib malate capsules based on linear pharmacokinetic performance across the strengths to-be-marketed, the high solubility across the pH range of pH 1.2 to pH 6.8, and the in vitro dissolution comparison of the profiles generated for three 25-mg commercial batches and the 50-mg clinical trial formulation. A comparability analysis indicated that the formulations have comparable dissolution profiles.

Following oral administration, sunitinib is slowly absorbed from the gastrointestinal tract with maximum concentrations observed from 6 to 12 hours after dosing. The pharmacokinetic profile is comparable for sunitinib when administered as a capsule or as an oral solution. Administration of sunitinib in the presence or absence of food has no effect on the PK profile of sunitinib. Therefore, sunitinib can be administered without regard to meals. Plasma protein binding of sunitinib is 95% and that of the active metabolite is 90%.

Sunitinib is metabolized via CYP3A4 mediated de-ethylation to the active equipotent metabolite SU012662. AUC of the active metabolite is approximately 23-37% of the parent. The terminal half-lives of sunitinib and SU012662 are approximately 40 to 60 hours and 80 to 110 hours, respectively. Steady-state conditions of sunitinib and

SU012662 are reached in approximately 2 weeks.

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

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

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

In the GIST patients, there was a significant relationship between TTP and exposure. A significant relationship was also seen for partial response rates and exposure in these patients. Increased AUC was associated with longer time to tumor progression, and with higher rates of partial responses. In the MRCC patients, there was no apparent relationship between TTP and exposure or between partial response rates and exposure in the MRCC patients. Additional analyses examined the influence of baseline tumor size on response as well as the effect of exposure on changes in tumor size. These analyses also showed that while increased exposure was associated with larger changes in tumor size for the GIST patients, no relationship was apparent in the MRCC patients.

Exposure-response relationships were also developed for the frequency of severe (grade 3 or 4) adverse events seen across the GIST, MRCC and solid tumor studies. Significant relationships were obtained for the incidence of severe fatigue, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction

dysfunction. There was no additional effect of gender on the exposure-toxicity relationships.

OCPB Briefing held on Jan 5, 2005.

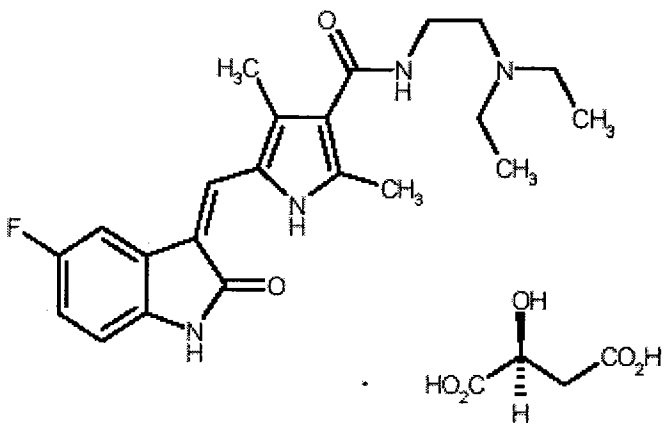
Attendees present included Sophia Abraham, Carol Noory, Joga Gobburu, Brian Booth, Roshni Ramchandani, Shiew-Mei Huang, John Hunt, Mehul Mehta, Lawrence Lesko, Chandra Sahajwalla, Robert Powell, Ramzi Dagher, Edwin Rock, Vicki Goodman

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.



Sunitinib **L-malate counter ion**

Figure 1. Chemical Structures of Sunitinib and L-Malate Counter Ion.

Molecular weight: 398 Daltons (sunitinib), 523 Daltons (sunitinib malate)
Molecular formula: $C_{22}H_{27}FN_4O_2$ (sunitinib), $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ (sunitinib malate)

There are no chiral centers in sunitinib. The optical rotation observed for sunitinib malate is due to the L-malate counterion only. Sunitinib malate has a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2-6.8 is 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2. Sunitinib malate is supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg, and 50 mg of sunitinib (free base).

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 (Table 1). The primary metabolite of sunitinib, SU012662, exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Table 1. Inhibition of Target Receptor Tyrosine Kinases by Sunitinib

Tyrosine Kinase	Biochemical K_i[a] (μM)	Cellular IC_{50} (μM)	
		RTK Phosphorylation[b]	Cell Proliferation[d]
VEGFR1	0.002	ND	ND
VEGFR2	0.009	0.01	0.004
VEGFR3	0.017	ND	ND
PDGFRα	ND	ND	0.069
PDGFRβ	0.008	0.01[c]	0.039
KIT	ND	0.001-0.01[c]	0.002
FLT3	ND	0.25	0.01-0.1
FLT3-ITD	ND	0.05[c]	0.01-0.05
RET	ND	0.05[c]	0.05
CSF-1R	ND	0.05-0.1[c]	ND
FGFR1	0.83	ND	0.88

ND = not determined; ITD = internal tandem duplication;
[a] Values were determined in biochemical kinase assays using recombinant enzymes.
[b] Values were determined by measuring intrinsic or ligand-stimulated kinase activity (phosphorylation) in cell lines expressing a given target RTK by immunoblot[c] or ELISA assay.
[c] Values (or value ranges) were estimated from immunoblot analysis of RTK phosphorylation over a range of concentrations.
[d] Values were determined by measuring intrinsic or ligand-stimulated cell proliferation in cell lines expressing a given target RTK.

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).

The proposed indications for sunitinib are: 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 following table summarizes the studies included in the PK analysis. The applicant has conducted a population PK analysis incorporating data across all these studies to characterize the PK of sunitinib and its metabolite, and examined the impact of several intrinsic covariates on the PK parameters for sunitinib.

Table 2. Summary of sunitinib studies included in PK analysis.

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

RTKC-0511-016	Open-label, non-randomized study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50 mg Oral Repeat doses QD on schedule 2/16	12
RTKC-0511-018	Open-label, dose escalation study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50-175 mg loading dose on day 1 50 mg Oral Repeat doses QD on schedule 2/1	27

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

The following table summarizes the phase 2 and 3 studies included in the PK-PD analysis of efficacy and safety of sunitinib in GIST and MRCC patients. The dose of sunitinib was selected based on maximally tolerated doses in the early phase 2 studies (study 002, 005 and 013).

Table 3. Summary of sunitinib studies included in PK-PD Analysis.

Protocol	Design	Treatment Duration	# Patients Enrolled	Doses	PK Sampling	PD Evaluation	Formulation
248-ONC-0511-002 (Study 002)	dose escalating study in patients with advanced solid tumors	6 week cycles on Schedule 4/2 (4 weeks on drug followed by 2 weeks rest period)	28	25 - 150 mg QD or QOD with dose escalation	full PK profiles taken on day 1 and day 28. at 1,2,3.5,4.5,6.5,7,8 ,10,12, 14,and 16 hours after dosing; trough level on day 2 and 29 and twice weekly during the first cycle.	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies, and clinical assessments weekly. Electrocardiographic assessment, hematology and blood chemistry performed pre-study and twice weekly	Free-base and L-malate salt capsule
RTKC-0511-005 (Study005)	dose escalating study in patients with solid cancer cancer	6 week cycles on Schedule 4/2 or 4 week cycles on Schedule 2/2 (weeks on/off)	42	25-75 mg QD or QOD with dose escalation	full PK profiles taken on day 1 and day 28 at 1,2,3.5,4.5,6.5,7,8 ,10,12, 20, 24, and 48 hours after dosing; trough level twice weekly during the first cycle	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies, and clinical assessments weekly. Electrocardiographic assessment, hematology and blood chemistry performed pre-study and weekly	Free-base and L-malate salt capsule
RTKC-0511-013 (Study 013)	open-label, dose-escalating study in GIST patients	6 week cycles on 4/2, 4 week cycles on 2/2, or 3 week cycles on 2/1 (weeks on/off)	97	25 -75 mg QD with dose escalation.	1,4,6,8,10,12,24, and 48 hours post-dose from 18 patients. Trough levels were taken from all patients on days 1,14, and 28	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies, and clinical assessments at day 14 and 28 of cycle 1, day 28 of each additional cycle	L-malate salt capsule

A6181004 (Study 1004)	dual-arm, double-blind, placebo-controlled, multicenter, clinical trial with 2:1 randomization in GIST patients	6 week cycles on Schedule 4/2	357*	50 mg QD, with dose reduction to 37.5 and 25 mg if needed. Dose range: 25-50 mg QD	Trough sampling at day 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 day 14 and 28 of cycle 1, day 28 of each additional cycle	L-malate salt capsule
RTKC-0511-014 (Study 014)	open-label, single-arm, multicenter, clinical trial evaluating the efficacy and safety as single-agent, second-line therapy in RCC patients	6 week cycles on Schedule 4/2	63	50 mg QD with dose reduction if needed. Dose range: 25-62.5 mg QD	Trough sampling at day 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 day 14 and 28 of cycle 1, day 28 of each additional cycle	SU011248 L-malate salt capsule
A6181006 (Study 1006)	open-label, single-arm, multicenter, trial evaluating the efficacy and safety as a single-agent in RCC patients	6 week cycles on Schedule 4/2	106*	50 mg QD. Dose range: 25-62.5 mg QD	Trough sampling at day 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 day 14 and 28 of cycle 1, day 28 of each additional cycle	L-malate salt capsule

RECIST = Response Evaluation Criteria In Solid Tumors
QD = once daily dosing
QOD=every other day dosing
* Not all patients and data were available for this analysis, as data was cut off as of December 1, 2004.

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?

The response measures for efficacy included time to tumor progression (primary endpoint for GIST studies), objective response rates (primary endpoint for MRCC studies) as well as overall survival.

Several measures of toxicity were also evaluated as a function of exposure to sunitinib and its metabolite. These included: fatigue, nausea, vomiting, neutropenia, thrombocytopenia, anemia, pancreatic dysfunction, hypertension, and LVEF dysfunction.

The Pharmacometrics Review (Section 5) provides a detailed description of the measures of efficacy and toxicity.

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.

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 (see figures 2 and 4).

There were 2 principal measures of effectiveness: time to tumor progression (TTP), which was the primary endpoint for GIST and objective response rate, which was the primary endpoint for MRCC.

Time to Tumor Progression

Kaplan-Meier curves were plotted for TTP in patients classified based on an AUC median split, separately for the GIST and MRCC patients. The same relationships were also examined using AUC of the parent drug only.

In the GIST studies, patients on sunitinib had longer TTP than patients on placebo, and patients with higher AUCs had longer TTP compared to patients with low AUCs.

Cox proportional hazards analysis indicated a significant effect of total AUC on the risk for tumor progression with a hazard ratio for AUC of 0.51, indicating a ~50% decrease in risk of progression for each unit increase in AUC.

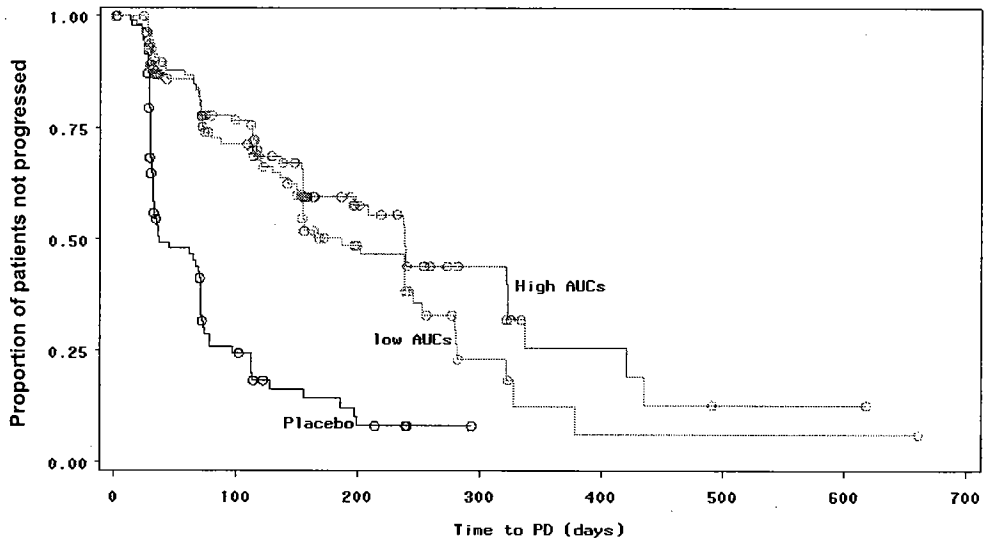


Figure 2a: Kaplan-Meier curves for time to tumor progression in GIST patients on placebo and on sunitinib, classified based on the ***combined parent + metabolite AUC*** *median split.*

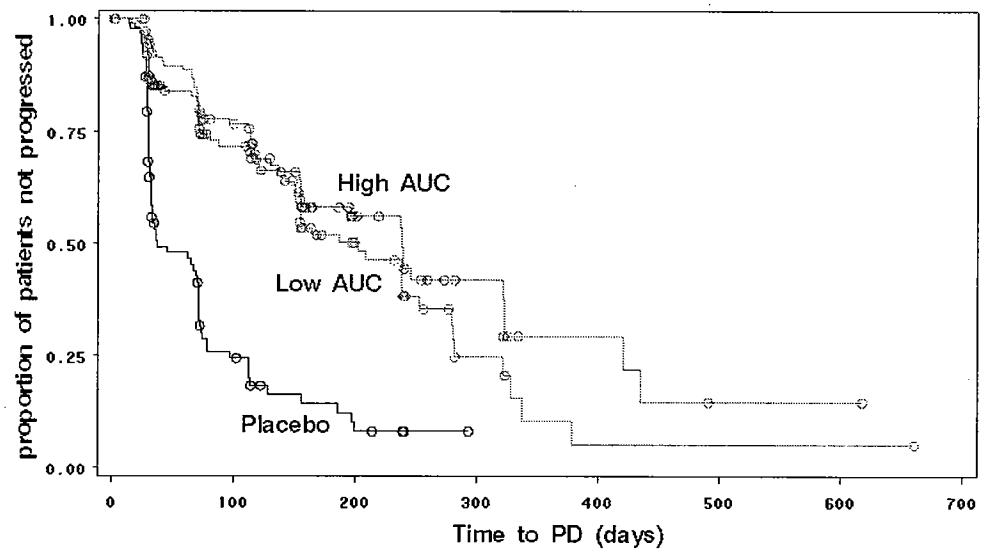


Figure 2b: Kaplan-Meier curves for time to tumor progression in GIST patients on placebo and on sunitinib, classified based on the ***parent drug only (sunitinib)*** *AUC median split.*

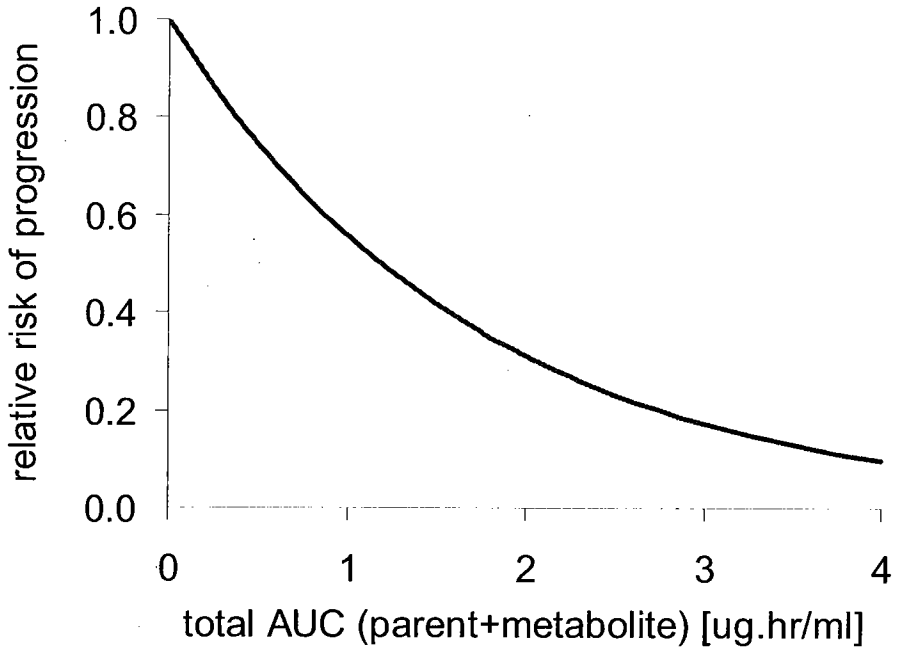


Figure 3: Risk of tumor progression vs. combined parent +metabolite AUC (sunitinib+SU012662) in GIST patients, obtained from COX proportional hazards analysis.

In the MRCC studies, Kaplan-Meier curves did not indicate a consistent exposure-response relationship. Using only parent AUC or combined parent+metabolite AUC gave the same results.

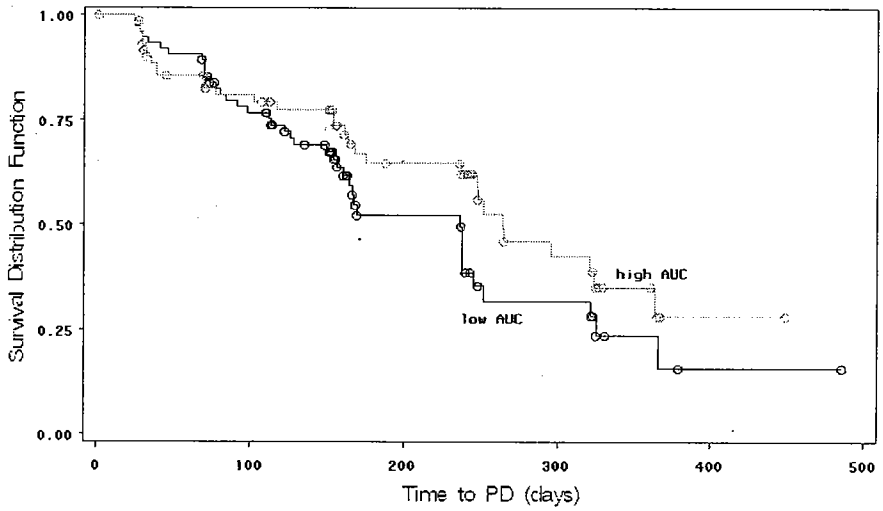


Figure 4a: Kaplan-Meier curves for time to tumor progression in MRCC patients on sunitinib, classified based on the **combined parent+metabolite *AUC*** *median split.*

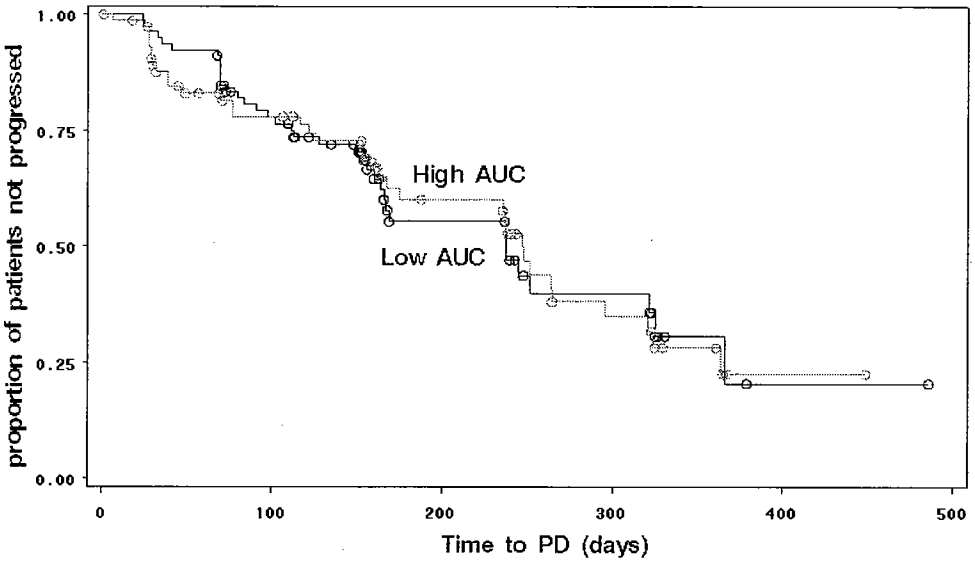


*Figure 4b: Kaplan-Meier curves for time to tumor progression in MRCC patients on sunitinib, classified based on the **parent drug AUC** median split.*

In addition to this, the applicant analyzed the TTP data using a parametric method, where the TTP data was fit to a Weibull distribution function, and the hazard function was modeled as a function of exposure. However, the applicant combined the data across tumor types, which did not allow the evaluation of any tumor-type-related differences. The Agency has repeated this analysis, separately for each tumor type and the results are included in the Pharmacometric Review. In summary, the parametric analysis results were consistent with the non-parametric analysis shown above. For GIST, there was a significant effect of exposure on the lambda (or hazard function). Using treatment or AUC gave similar results, indicating that increased exposure is associated with a longer time to tumor progression. In MRCC patients, a significant relationship was seen for AUC and risk for progression, but the relationship was very shallow.

Response Rates

The following figures show the results of logistic regression of the response rates for partial responses as a function of total AUC. Partial response rates were evaluated since no complete responses were seen in these studies.

In the GIST studies, a significant relationship was seen in the probability of partial responses and the total AUC. Increased exposure was associated with increased response rates for partial responses in GIST patients.

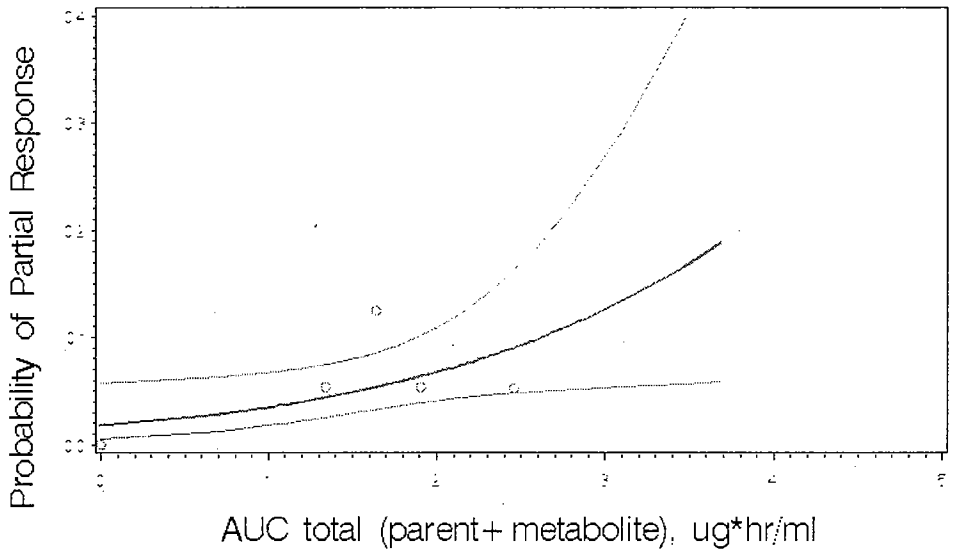


Figure 5: Probability of partial responses (based on RECIST criteria) vs. combined AUC (parent+metabolite) for patients with GIST.

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

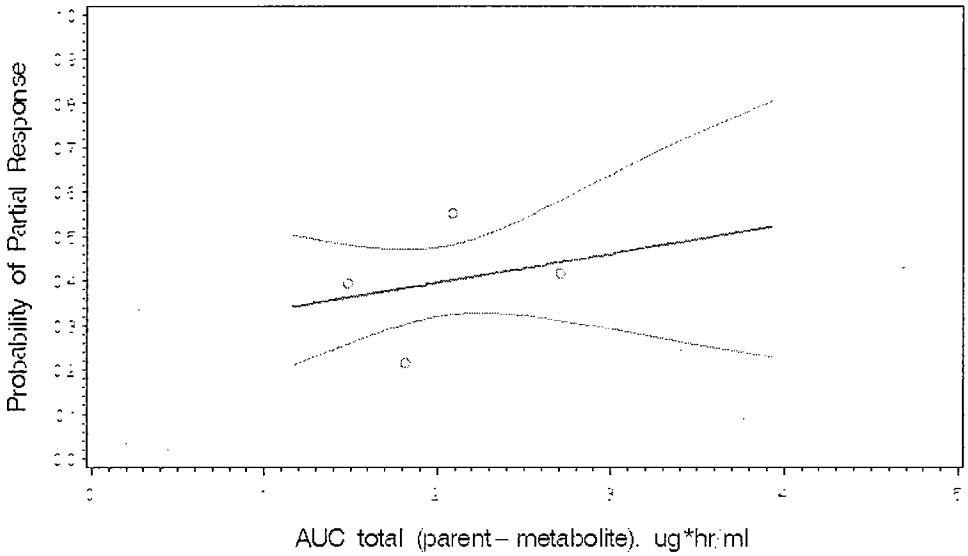


Figure 6: Probability of partial responses (based on RECIST criteria) vs. combined AUC (parent+metabolite) for patients with MRCC.

Effect of adjusting exposures for differences in plasma protein binding

It was of interest to examine if adjusting the parent drug and metabolite exposures for their respective plasma protein binding provided any additional value than using exposures of total (free+bound) drug and metabolite in E-R relationships. When the combined AUC (parent and metabolite) was calculated for free (unbound) drug and used in the analysis, no differences in outcome was achieved. Both measures of exposure showed almost identical effects on time to tumor progression in GIST and objective response rates in MRCC. This is illustrated in the following figures which show Kaplan-Meier curves for time to progression in GIST and MRCC for patients classified on the basis of free (unbound) combined drug and metabolite AUCs. Comparison of these figures with figures 2 and 4 indicate the similarity in the exposure-response relationship regardless of measure of exposure used in the analysis.

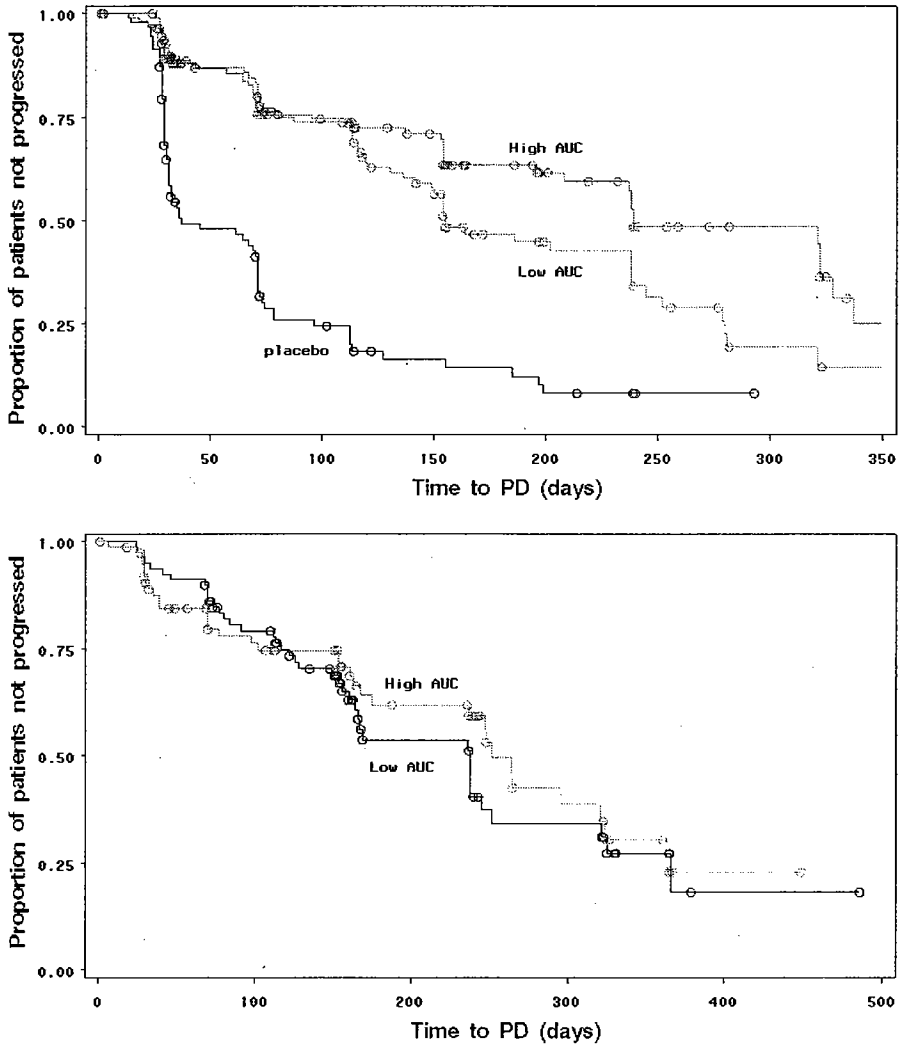


Figure 7: Kaplan-Meier curves for time to tumor progression in GIST patients (upper panel) and MRCC patients (lower panel) on sunitinib, classified based on a median split of ***unbound combined AUC (sunitinib+SU012662).***

Changes in Tumor Size

Figure 8a shows the % change in tumor size in GIST patients (placebo and sunitinib). The plots highlight the difference in tumor size changes, with a greater proportion of sunitinib patients showing decreases in tumor size than in the placebo group. Figure 8b shows a similar plot for the MRCC patients, and illustrates the large proportion of patients that showed decreases in tumor size.

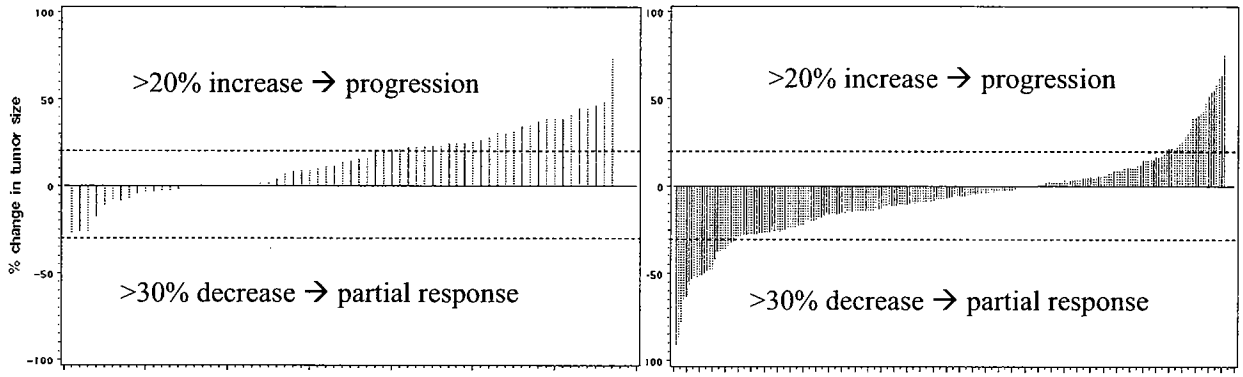


Figure 8a: Percent change in tumor size in placebo patients (left panel) and sunitinib patients (right panel) with GIST.

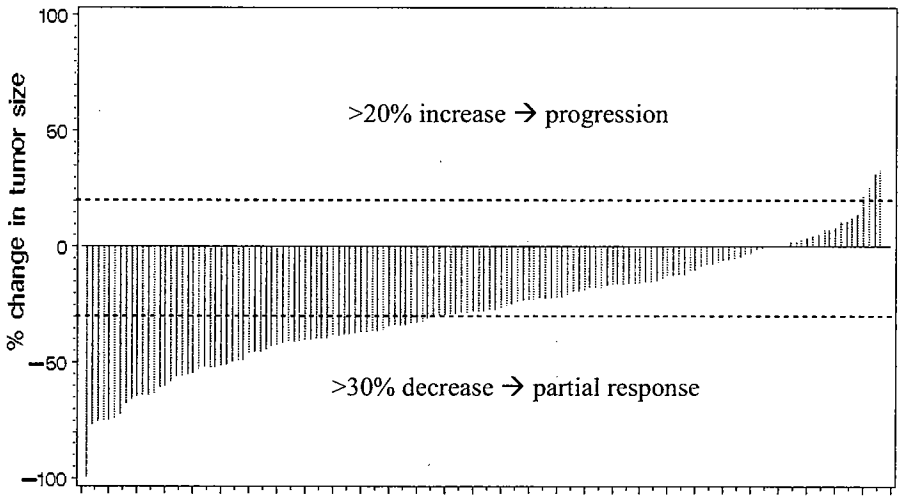


Figure 8b: Percent change in tumor size in sunitinib patients with MRCC.

Additional analyses were conducted to examine the influence of baseline tumor size on response as well as the effect of exposure on changes in tumor size. Details of the analysis are included in the Pharmacometric Review. These analyses showed that (1)

there were no differences in baseline tumor size as a function of exposure across the GIST or MRCC patients. (2) Increased exposure was associated with larger changes in tumor size for the GIST patients, no relationship was apparent in the MRCC patients (figures 9 and 10 respectively).

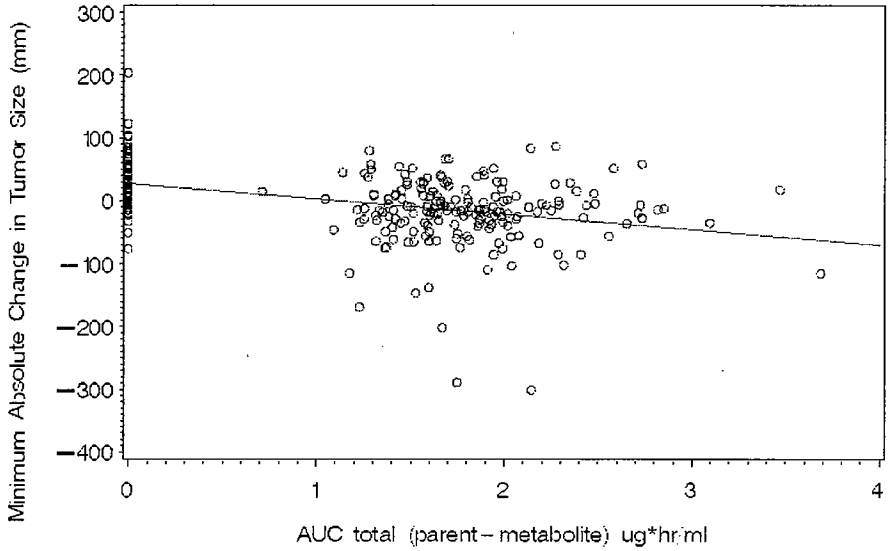


Figure 9: Largest change in absolute tumor size post-treatment as a function of combined AUC (parent+metabolite) in GIST patients. Straight line shows the regression line for the significant relationship.

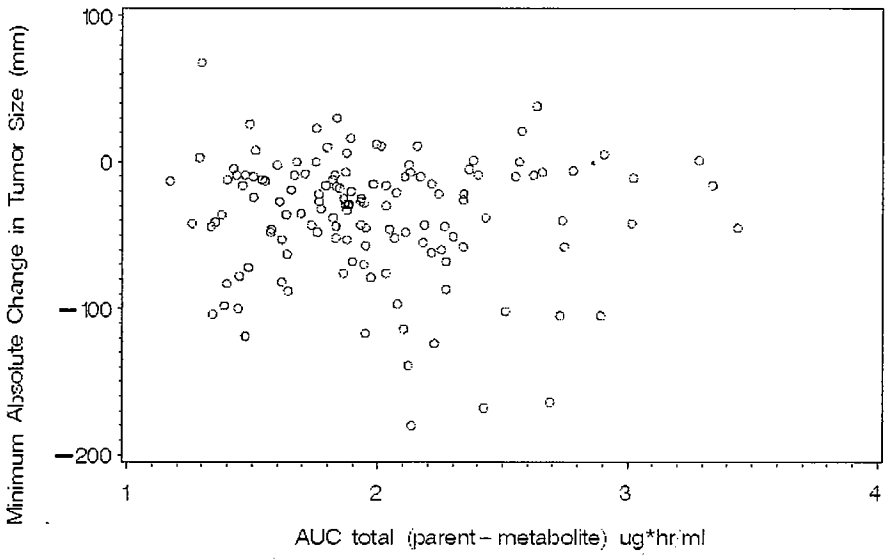


Figure 10: Largest absolute change in tumor size post-treatment as a function of combined AUC (parent+metabolite) in MRCC patients, showing the lack of significant association between exposure and largest absolute change in tumor size.

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. The toxicity data was evaluated for all the above adverse events, using logistic regression. The frequency of severe grade 3/4 toxicity for all the above measures (except nausea and vomiting where all grades were included and hypertension where grade 2/3 toxicity was used) was modeled as a function of combined AUC (parent+metabolite). The effect of sex, tumor type (GIST, MRCC, solid tumors) and ECOG score was also examined in these models.

Additional analyses were performed for fatigue, absolute neutrophil counts, blood pressure and LVEF. Each of these measures was analyzed as continuous variables as functions of exposure (AUC or trough concentrations) along with covariates including sex, ECOG score and tumor type. These analyses are described in detail in the Pharmacometrics Review.

The following table gives a summary of the results.

Table 4: Incidence of severe (grade 3/4) toxicity with sunitinib and odds ratio for effect of exposure.

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

The following figure shows a composite of the predicted probabilities for the various toxicities as a function of exposure.

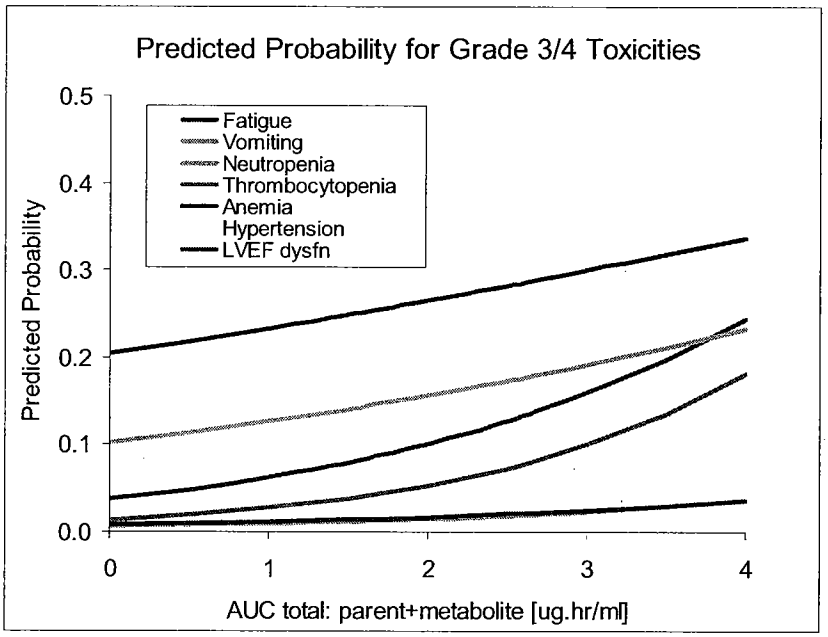


Figure 11: Predicted probability of severe grade 3/4 toxicities vs. combined AUC (parent+metabolite) in GIST and MRCC patients.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Preclinical studies have shown sunitinib to inhibit the hERG potassium channel current (IC50=0.27 µM or 108 ng/mL) and to prolong the action potential duration in dog Purkinje fibers (at concentrations above 1 µM or 400 ng/mL). Also, SU012662 inhibited the hERG potassium channel current (IC50=4.1 µM or 1500 ng/mL). The combined parent+metabolite steady-state peak plasma levels following a 50 mg regimen (daily on a 4weeks on - 2 weeks off schedule) ranged from 75-126 ng/ml. Given that sunitinib and SU012662 are highly protein bound (90-95%), unbound levels of parent+metabolite would be expected to be much lower than the IC50s of 108 and 400 ng/ml seen in the *in vitro* studies.

In addition to the *in vitro* results, QT interval prolongation was observed in monkeys receiving single high doses (50 or 150 mg/kg) of sunitinib. The no-observed-effect level for this effect was 15 mg/kg, which is above the no-observed-adverse-effect level determined in repeated-dose toxicity studies. No other effects on QT interval were observed in the cardiovascular, respiratory, or central nervous system safety pharmacology studies.

As part of subject safety evaluation in almost all the clinical studies of sunitinib, ECGs were recorded to assess the potential of sunitinib to prolong the QT interval. The following tables show the number of patients with maximum QTc values and maximum changes in QTc interval from baseline in GIST, MRCC and other tumor types.

Table 5: QTc interval data from GIST studies.

QTc Category	Study RTKC-0511-013	Study A6181004		Pooled
		Sunitinib Treatment	Placebo Treatment	
Maximum postbaseline QTc value, N	54	157	80	211
≤450 msec	52 (96.3)	143 (91.1)	77 (96.3)	195 (92.4)
>450-470 msec	2 (3.7)	11 (7.0)	2 (2.5)	13 (6.2)
>470-500 msec	0 (0)	2 (1.3)	1 (1.3)	2 (0.9)
>500 msec	0 (0)	1 (0.6)	0 (0)	1 (0.5)
Maximum change in QTc from baseline, N	54	157	78	211
≤30 msec	53 (98.1)	145 (92.4)	73 (93.6)	198 (93.8)
>30 - <60 msec	1 (1.9)	8 (5.1)	5 (6.4)	9 (4.3)
≥60 msec	0 (0)	4 (2.5)	0 (0)	4 (1.9)

Table 6: QTc interval data from MRCC studies.

QTc Category	No. of Subjects, n (%)		
	Study RTKC-0511-014	Study A6181006	Pooled
Maximum postbaseline QTc value, N	60	85	145
≤450 msec	57 (95.0)	82 (96.5)	139 (95.9)
>450-470 msec	1 (1.7)	2 (2.4)	3 (2.1)
>470-500 msec	2 (3.3)	1 (1.2)	3 (2.1)
>500 msec	0 (0)	0 (0)	0 (0)
Maximum change in QTc from baseline, N	60	85	145
≤30 msec	54 (90.0)	80 (94.1)	134 (92.4)
>30 - <60 msec	6 (10.0)	5 (5.9)	11 (7.6)
≥60 msec	0 (0)	0 (0)	0 (0)

Table 7: QTc interval data from all solid tumor studies and AML study.

QTc Category	No. of Subjects, n (%)		
	Solid Tumors (includes GIST, MRCC and other solid tumors across studies)	AML	All
Maximum postbaseline QTc value, N	378	9	387
≤450 msec	350 (92.6)	7 (77.8)	357 (92.2)
>450-470 msec	19 (5.0)	1 (11.1)	20 (5.2)
>470-500 msec	7 (1.9)	1 (11.1)	8 (2.1)
>500 msec	2 (0.5)	0 (0)	2 (0.5)
Maximum change in QTc from baseline, N	376	8	384
≤30 msec	350 (93.1)	7 (87.5)	357 (93.0)
>30 - <60 msec	22 (5.9)	1 (12.5)	23 (6.0)
≥60 msec	4 (1.1)	0 (0)	4 (1.0)

As the tables above show, 2 patients had maximum post-baseline QTc value>500 (maximum QTc values of 509.5 and 510 msec) and 4 patients showed maximum change in QTc ≥ 60 msec (maximum change in QTc intervals of 77.6, 79.5, 88.0 and 96.6 msec). It should be noted that in most studies, the applicant did not provide the method of correction of the QT interval as it was not documented by investigators during the studies.

In addition to the analyses above, the Agency has combined the data from clinical safety summary of the solid tumor, GIST and MRCC studies (6 studies, n=639) and plotted the maximum QTc value and change in QTc interval vs. total AUC of sunitinib and SU012662. The plots, shown below, do not demonstrate any relationship between maximum post-baseline QTC interval and exposure, or maximum change in QTc interval and exposure.

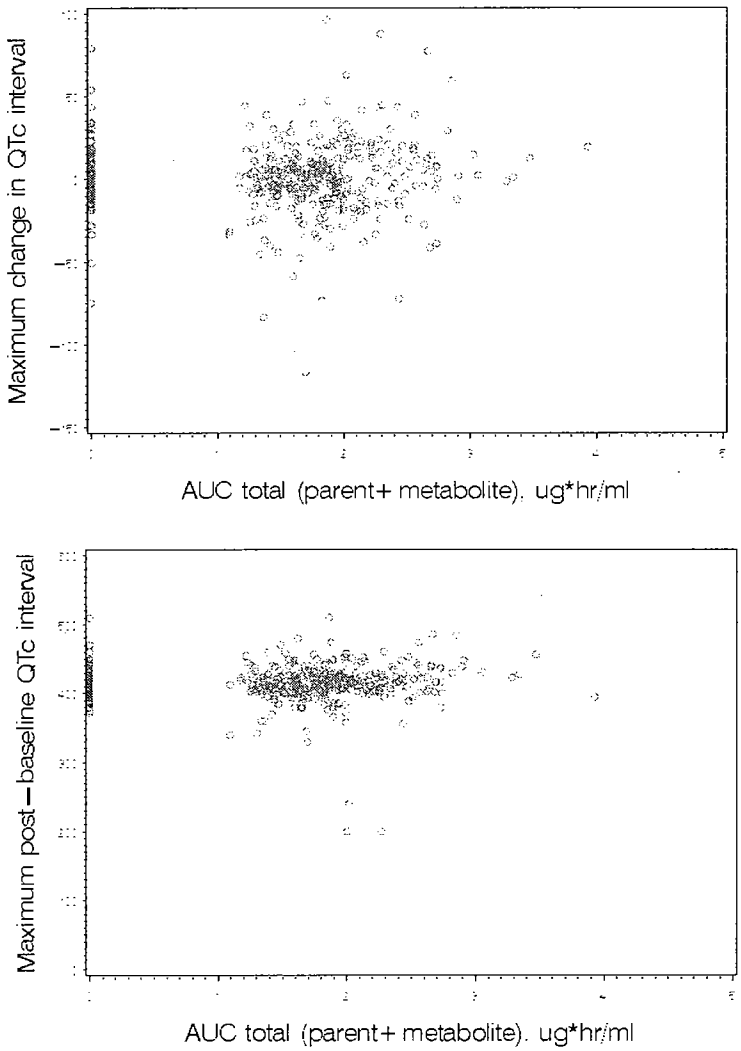


Figure 12: Maximum post-baseline QTC interval vs. total AUC (upper panel), and Maximum change in QTc interval vs. total AUC (lower panel) for GIST and MRCC patients.

In summary, while 4/378 patients in the clinical trials did show QTC prolongation, there was no consistent relationship of these changes with exposure or among tumor types. Therefore the clinical significance of this remains unknown.

The sponsor has begun a "thorough" QTc study (A6181005), which is a single-blind, nonrandomized, 3-treatment, dose-escalating, single-center trial in subjects with advanced solid malignant tumors, which includes a placebo control and a positive control (moxifloxacin). This study is powered to detect a change in QTc interval of 8 msec (a minimum of 30 subjects with available data for evaluation were required for this analysis). To ensure that a combined (sunitinib + its active metabolite, SU012662) plasma concentration of at least 200 ng/mL is achieved (a concentration that may result from CYP3A4 inhibition of 50% as seen in the drug-drug interaction study with ketoconazole), the design of this protocol provides for the loading sunitinib doses of 150 to 225 mg at the beginning and the end of a 1-week 50-mg QD dosing regimen (the loading doses were used to minimize safety risk resulting from prolonged exposure to high plasma concentrations of sunitinib + SU012662). Serial triplicate ECGs are recorded at baseline and after administration of moxifloxacin, placebo, and sunitinib (time-matched). All ECGs will be measured manually at the central ECG laboratory. QT intervals will be corrected for heart rate using Fridericia's correction (QTcF).

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?

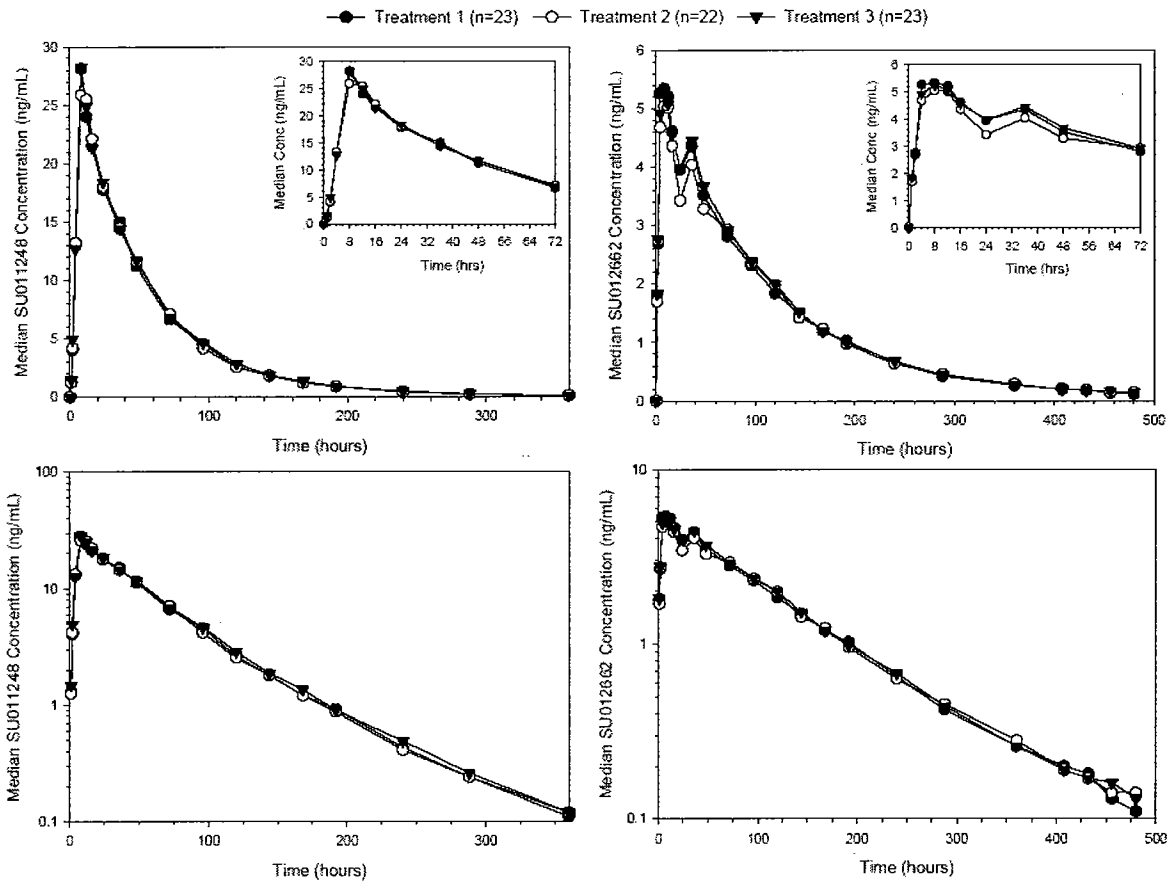
The registration studies for both GIST and MRCC used only one dose level, i.e. 50 mg daily for 4 weeks of a 6-week cycle. This dose was selected primarily based on safety as dose-limiting toxicities were seen in the phase 1 studies at the next dose level of 75 mg. Based on the results of the registration studies, it appears that the 50 mg dose results in a ~70% reduction in the risk of tumor progression in GIST patients, and results in a 25-35% response rate for partial responses in MRCC patients. In both tumor types, there were a proportion of patients who required dosing delays or reductions due to toxicity. Dose reductions were seen in 11-12% of GIST patients and 22-40% of MRCC patients. As there is no clinical effectiveness data at other dose levels, it is unclear if this dose level is optimal.

Significant exposure-response relationships were developed for TTP in the GIST patients at this dose level. However, there was no apparent exposure-response relationship for partial response rates in the MRCC patients at this dose level, although the response rates were relatively high across the range of exposures seen in these patients. Exposure-toxicity relationships were obtained for several of the toxicity measures across the tumor types.

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?

Figure 13 shows the plasma concentration vs. time profiles for sunitinib and SU012662 in healthy volunteers following single 50 mg doses.



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).

Figure 13: Concentration – time profiles for sunitinib and SU012662 following single doses in healthy subjects (study A6181033). Upper panels: linear scale, Lower panels: log scale.

The following table summarizes the PK parameters for sunitinib and SU012662 in healthy subjects following a single dose of sunitinib.

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Table 8: Summary of sunitinib and SU012662 PK parameters in healthy subjects by study and treatment group following single doses of sunitinib.

Parameter	Statistic	Study 001	Study 004		Study 009	Study 1001	Study 1031	Study 1032	Study 1033			Study 1046	
			Trt. A	Trt. B				Fasted	Trt. 1	Trt. 2	Trt. 3	Trt. 1	Trt. 2
		50 mg (n = 6)	50 mg (n = 14)	50 mg (n = 13)	10 mg (n = 27)	50 mg (n = 25)	50 mg (n = 6)	50 mg (n = 16)	50 mg (n = 23)	50 mg (n = 22)	50 mg (n = 23)	12.5 mg (n = 16)	12.5 mg (n = 16)
Sunitinib													
C_{max}[a] (ng/mL)	Mean	37.7	24.1	25.5	23.8	30.1	24.4	26.3	31.5	31.0	31.3	23.0	22.4
	%CV	25	26	24	23	24	16	32	38	36	32	25	24
AUC_{0-last}[a] (ng*hr/mL)	Mean	943	996	1108	1267	1318	1052	1534	1582	1575	1556	1373	1374
	%CV	25	35	35	37	23	25	28	35	35	32	22	24
$AUC_{0-\infty}$[a] (ng*hr/mL)	Mean	1350	1029	1131	1318	1328	1063	1546	1592	1587	1566	1418	1418
	%CV	32	34	36	36	23	25	28	34	35	31	22	24
T_{max} (hr)	Median	6	7	6	8	8	8	8	8	8	8	12	12
	Min, Max	5, 16	4.5, 10	4.5, 12	5, 16	7, 12	8, 8.1	8, 16	8, 12	8, 12	8, 12	8, 16	8, 16
$T_{1/2}$ (hr)	Mean	26.9	38.1	39.0	42.2	48.9	50.9	60.0	51.7	52.0	51.9	55.6	53.7
	%CV	27	23	16	20	23	13	18	21	24	21	23	24
CL/F (L/hr)	Mean	40.4	54.3	50.9	42.7	39.5	49.9	35.0	34.3	34.8	34.6	37.0	37.2
	%CV	32	35	42	35	21	28	30	27	31	28	24	24

Parameter	Statistic	Study 001	Study 004		Study 009	Study 1001	Study 1031	Study 1032	Study 1033			Study 1046	
			Trt. A	Trt. B				Fasted	Trt. 1	Trt. 2	Trt. 3	Trt. 1	Trt.2
		50 mg (n = 6)	50 mg (n = 14)	50 mg (n = 13)	10 mg (n = 27)	50 mg (n = 25)	50 mg (n = 6)	50 mg (n = 16)	50 mg (n = 23)	50 mg (n = 22)	50 mg (n = 23)	12.5 mg (n = 16)	12.5 mg (n = 16)
SU012662													
C_{max}[a] (ng/mL)	Mean	6.46	5.47	5.18	3.00	6.20	6.15	4.89	6.21	5.81	6.17	3.20	3.40
	%CV	26	29	24	23	30	29	42	46	39	40	27	29
AUC_{0-last}[a] (ng*hr/mL)	Mean	183	362	373	301	588	575	599	702	666	700	460	484
	%CV	26	38	32	31	28	16	31	41	39	41	21	33
$AUC_{0-\infty}$[a] (ng*hr/mL)	Mean	444	418	438	384	609	593	631	722	688	721	540	563
	%CV	38	38	34	26	27	15	30	40	38	41	21	29
T_{max} (hr)	Median	5	5	5	7	7	6	12	8	8	8	18	26
	Min, Max	4.5, 24	0, 6.5	4.5, 12	4, 72	4, 24	4, 12	4, 36	4, 36	2, 36	4, 36	2, 144	4, 72
$T_{1/2}$ (hr)	Mean	57.5	71.1	77.6	82.7	78.5	93.2	106	88.3	90.6	88.1	108	107
	%CV	63	26	24	19	20	17	21	15	16	13	30	30

Source: Tables A-5.1.1 and A-5.1.2, and clinical study reports for A6181032 (Study 1032) Tables 13.5.2 and 13.5.3, A6181033 (Study 1033) Tables 13.5.2 and 13.5.3, and A6181046 (Study 1046) Tables 13.5.2 and 13.5.3.

%CV = Percent Coefficient of Variation; $AUC_{0-\infty}$ = Area Under the Plasma Concentration Time Curve From 0 Extrapolated to Infinity; AUC_{0-last} = Area Under the Plasma Concentration Time Curve From 0 to Time of the Last Measurable Concentration; CL/F = Oral Clearance; C_{max} = Maximum Concentration; $T_{1/2}$ = Terminal Half-Life; T_{max} = Time to Maximum Concentration; Trt. = Treatment.

Data shown are for the following sunitinib treatments:

Study 001: 50-mg sunitinib free-base; Study 004: 50-mg free-base fasted (Trt. A), 50-mg L-malate fasted (Trt. B); Study 009: 10-mg sunitinib L-malate alone; Study 1001: 50-mg sunitinib L-malate alone; Study 1031: 50-mg [^{14}C]-sunitinib L-malate; Study 1032: 50-mg sunitinib L-malate proposed commercial formulation (fasted); Study 1033: 50-mg sunitinib L-malate clinical trial formulation (Trt. 1), 50-mg sunitinib L-malate proposed commercial formulation (Trt. 2), Four x 12.5-mg sunitinib L-malate proposed commercial formulation (Trt. 3); Study 1046: 12.5-mg sunitinib L-malate clinical trial formulation (Trt. 1), 12.5-mg sunitinib L-malate proposed commercial formulation (Trt. 2).

[a] C_{max} and AUC parameters have been normalized to a 50-mg sunitinib dose, where appropriate

The following table summarizes the PK parameters for sunitinib and SU012662 in oncology patients following multiple doses of sunitinib.

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)	88.0 (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).

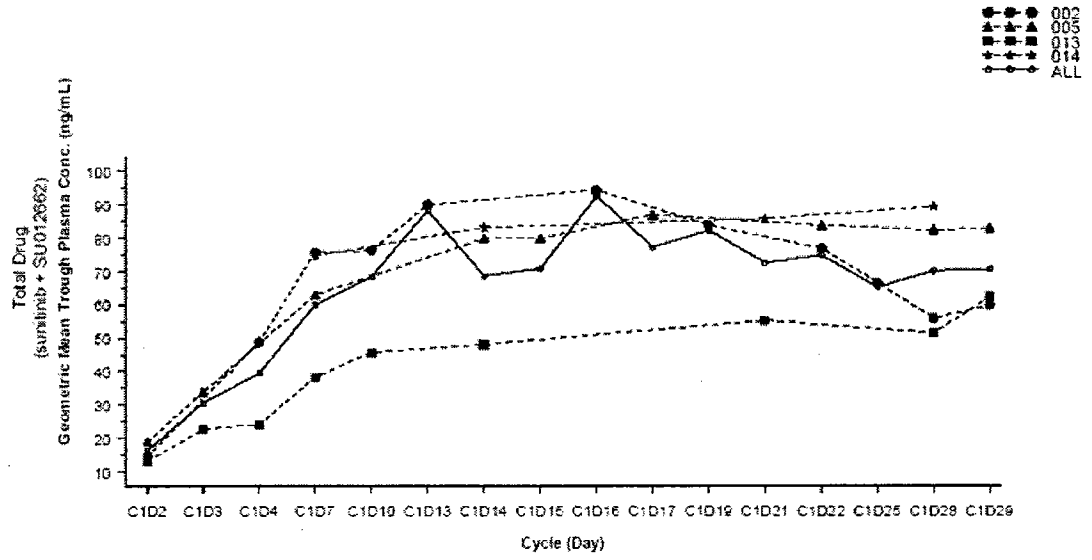


Figure 14: Geometric mean total drug (sunitinib + SU012662) trough concentrations following once daily dosing with 50 mg sunitinib (schedule 4/2).

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The following table provides a side-by-side comparison of PK parameters in healthy volunteers and in oncology patients. In general there were no differences in exposures between healthy subjects and patients, although the inter- and intra-subject variability was higher in the patients compared to the healthy subjects. This may be partially attributed to demographic differences that are not well-controlled in patient studies, but generally tightly controlled in healthy subject studies. Concomitant medications or the disease state itself may also have an impact.

Table 10: Comparison of sunitinib and SU012662 exposure and estimates of inter- and intra-subject variability in healthy subjects and oncology patients.

Analyte	Parameter[a] or Statistic	Range of Values[b]	
		Healthy Subjects	Patients
Sunitinib	C_{max} (ng/mL)	22.4-37.7	18.6-28.9
	AUC_{0-24} (ng*hr/mL)	384-523	299-430
	Inter-Subject (%CV)	24-33	31-38
	Intra-Subject (%CV)	5.1-9.8	29-38
SU012662	C_{max} (ng/mL)	3.00-6.46	1.90-6.00
	AUC_{0-24} (ng*hr/mL)	58.4-117	34.0-98.4
	Inter-Subject (%CV)	26-37	41-60
	Intra-Subject (%CV)	9.8-16.5	38-52

Source: Table 37 and Table 38, and statistical output from A6181032 (Appendices A10.2 and A10.3), A6181033 (Appendices A10.2 and A10.3), A6181046 (Appendices A10.2 and A10.3) and Appendix 2 of the SCP, ad hoc Tables 3 and 4.

%CV = %Coefficient of Variation; AUC_{0-24} = Area Under the Plasma Concentration Time Curve From 0 to 24 Hours; C_{max} = Maximum Concentration; PK = Pharmacokinetic.

[a] PK parameters are normalized to a 50-mg sunitinib dose, where appropriate.

[b] For the PK parameters (C_{max} and AUC_{0-24}), values presented are the range of means from multiple studies. For %CVs, values presented are the range of %CVs for the PK parameters (C_{max} and AUC_{0-24}), obtained from statistical models used in comparisons of data in healthy subjects and patients.

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 postdose following single and multiple doses. SU012662 peaked at approximately the same time as sunitinib, with median Tmax occurring at 6 to 12 hours postdose in most cases, though multiple peaking of SU012662 concentrations was observed in some studies, resulting in more variable or delayed Tmax estimates. However, this phenomenon had no significant effect on the extent of SU012662 AUC.

The absolute bioavailability of sunitinib has not been determined. The relative BA of sunitinib 50 mg administered orally as the free base versus the malate salt has been evaluated in a study in 15 healthy male volunteers (248-ONC-0511-004). The table below summarizes sunitinib PK parameters and results of statistical comparisons for the 2 treatments. The results showed that there are no significant differences in BA of sunitinib between the freebase and L-malate salt formulations. Ninety percent CIs for

comparisons of sunitinib Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ (salt/free-base) were within the 80% to 125% bioequivalence range. A preliminary evaluation of the effect of food was also examined, and the results showed no effect of food on the Cmax and AUC of sunitinib.

Table 11: Geometric mean PK parameters and 90% confidence intervals on ratio of PK parameter estimates for sunitinib administered as free base or as L-malate salt under fasted and fed conditions.

Parameter	Geometric Mean (95% CI)			90% CI on Geometric LS Mean Ratio [a]	
	Treatment A (n = 14)	Treatment B (n = 13)	Treatment C (n = 14)	B/A	C/B
Cmax(ng/mL)	23.3 (20.0, 27.2)	24.7 (21.1, 28.9)	27.1 (22.7, 32.4)	0.98, 1.15	0.95, 1.16
AUC0-last (ng*hr/mL)	937 (758, 1159)	1038 (820, 1313)	1177 (937, 1479)	1.02, 1.16	1.00, 1.18
AUC0-∞ (ng*hr/mL)	974 (796, 1192)	1059 (836, 1341)	1230 (964, 1570)	1.00, 1.14	1.00, 1.18
Tmax (hr)[b]	7.25 (4.50, 10.0)	6.00 (4.50, 12.0)	6.75 (3.50, 10.0)	N/A	N/A

Treatment A: sunitinib free-base (50 mg) fasted;
Treatment B: sunitinib L-malate salt (50 mg free-base equivalent) fasted;
Treatment C: sunitinib L-malate salt (50 mg free-base equivalent) fed.
a Results from repeated measures ANOVA with formulation and period as factors.
b Values presented are median (min, max).

2.2.5.4 What are the characteristics of drug distribution?

Protein Binding:

Sunitinib is highly bound to human plasma proteins; 95.2±1.6% bound at *in vitro* concentrations of 0.1-4.0 µg/ml (Report PDM-060). The primary active metabolite, SU012662, is 89.8±1.1% bound to human plasma proteins at *in vitro* concentrations of 0.1-4.0 µg/ml (Report PDM-061). The impact of differences in protein binding between parent and metabolite on the combined AUC of active moieties was evaluated by estimating the combined AUC of unbound parent and metabolite, and using this combined "unbound" AUC as the measure of exposure in the E-R analyses. Results showed no differences in E-R relationships when the AUC was adjusted for differences in protein binding of parent and metabolite.

Blood/Plasma Ratio (C_{RBC} /C_p):

The red blood cell (RBC) partition coefficient of sunitinib ($k_p = C_{RBC}/C_p$) between whole blood and plasma averages 1.4±0.3% at concentrations of 50-200 ng/ml, suggesting a weak association with human red blood cells.

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

The Applicant conducted a mass-balance study in 6 healthy male subjects (Study A6181031) in which each subject received a single oral 50 mg sunitinib capsule containing approximately 100 µCi of [^{14}C]-Sunitinib. Fecal excretion was the major route of elimination of the drug. The mean total radioactivity (% dose) recovered in both feces and urine was 77±8.8% over 21 days. Fecal and urinary recoveries accounted for 61±7.2% and 16±2.5% of the administered dose, respectively. Four components were identified in feces, including 2 major components (the metabolite, SU012662, and the parent drug) as well as 2 minor metabolites (a mono-oxygenated sunitinib and an unknown metabolite). Sunitinib and its active metabolite, SU012662, account for approximately 74% of the radioactivity in the pooled fecal sample.

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

Table 12: Mean ± SD (%CV) Plasma Pharmacokinetic Parameters for sunitinib and SU012662, and Total Plasma Radioactivity Following a Single Dose of 50 mg [^{14}C]-SU011248 (100 µCi) to 6 healthy Male Subjects

Parameter	Total Plasma Radioactivity	Plasma SUNITINIB	Plasma SU012662
C_{max} *(ng/mL)	69.7±17.5 (25%)	23.2±5.2 (22%)	6.3±1.5 (24%)
T_{max} (hr)	8.7±1.7 (18%)	8.0±0.05 (0.6%)	5.3±2.1 (39%)
AUCinf *(ng.hr/mL)	2419±943# (39%)	1024±255 (24%)	576±113 (19%)
t½ (hr)	24.6±12.0# (48%)	55.6±10.9 (19%)	88.7±15.6 (17%)
CL/F (L/hr)	25.2±15.8# (62%)	51.6±13.4 (26%)	--
V_d/F (L)	693±142# (20%)	4087±1085 (26%)	--

*C_{max} and AUCinf in ng-eq/ml and ng-eq.hr/ml, respectively for total radioactivity
#(n=4)

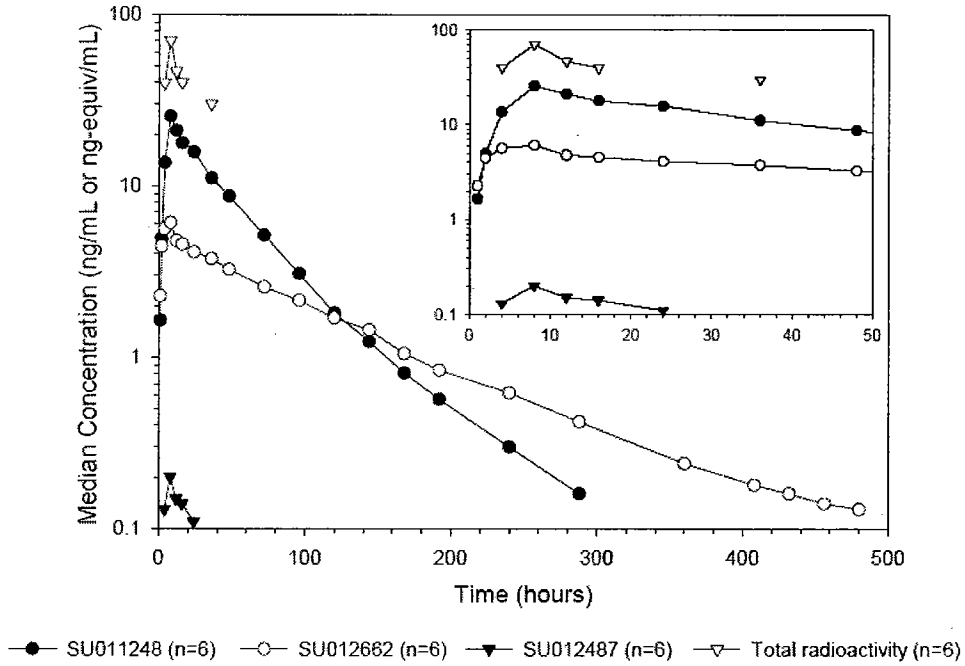


Figure 15: Mean Plasma Concentration/Time Profiles for Total Radioactivity, sunitinib and SU012662 Following a Single Dose of 50 mg [^{14}C]-SU011248 (100 µCi) to 6 Healthy Male Subjects

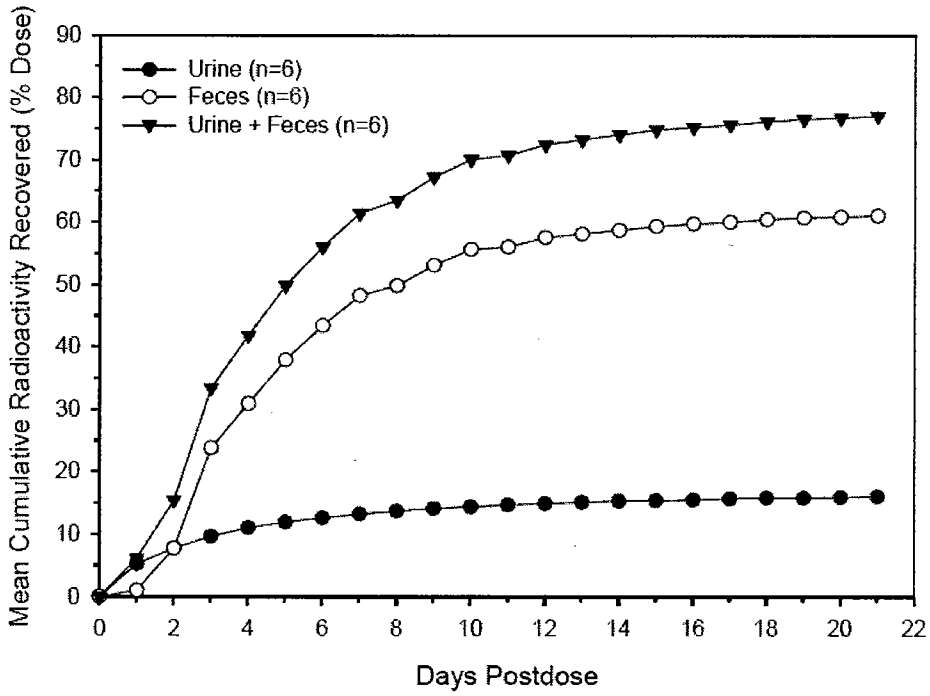


Figure 16: Mean cumulative radioactivity recovered as a function of time following a single dose of 50 mg [^{14}C]-SU011248 (100 µCi) to 6 healthy male subjects.

2.2.5.6 What are the characteristics of drug metabolism?

In vitro studies with human liver microsomes indicate that sunitinib (SU011248) undergoes CYP3A4-mediated N-de-ethylation to form a major, pharmacologic-ally active N-de-ethyl metabolite, SU012662 (Study SU011248-PDM-043). SU012662 undergoes further metabolism (N-de-ethylation), which is also primarily by CYP3A4 to form an inactive metabolite (SU014335), but at a much slower rate than the N-de-ethylation of sunitinib in human liver microsomes. Only trace amounts of other metabolites, including an N-oxide metabolite (SU012487), are formed *in vitro*. The formation of the N-oxide metabolite (SU012487) is catalyzed by flavin-containing monooxygenases (FMO). The percent of compound remained in incubation mixtures after 2 hours was 54.2% as parent drug, 41.6% as the N-de-ethyl metabolite, 1.12% as the N-oxide metabolite, and 3.1% as an unknown metabolite. The metabolic pathway of sunitinib in humans is shown in the figure below.

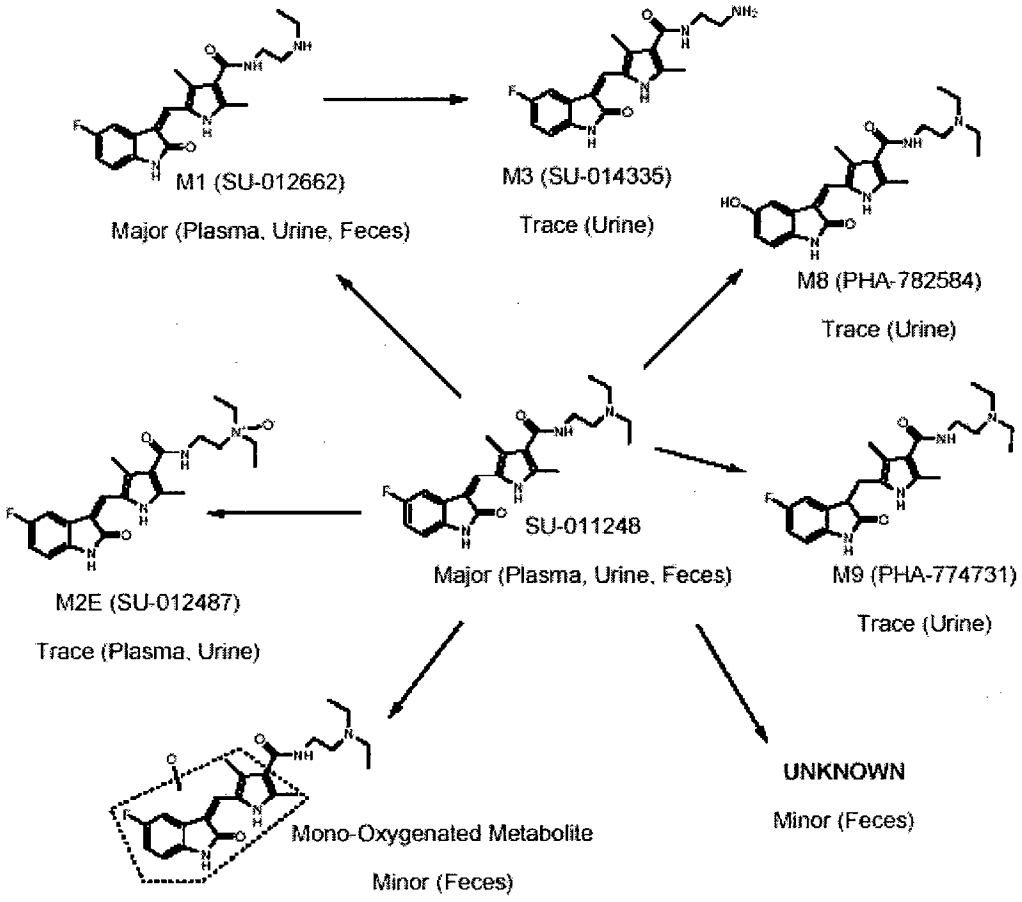


Figure 17: Proposed Metabolic Pathways of Sunitinib (SU011248) in Humans.

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.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose proportionality of sunitinib, SU012662, and total drug (sunitinib + SU012662) has been evaluated in oncology patients following single dosing with sunitinib doses ranging from 50 to 350 mg, and multiple (QD) dosing with doses of 25 to 100 mg (Schedule 4/2).
Comparison of dose-normalized Cmax and dose-normalized AUCs indicated that the PK of sunitinib and its primary metabolite SU012662 were dose-proportional in the range of doses evaluated. Log-log plots of Cmax vs. dose and AUC vs. dose had slopes close to 1 (see figure) also indicating that the PK of sunitinib and SU012662 are dose-proportional.

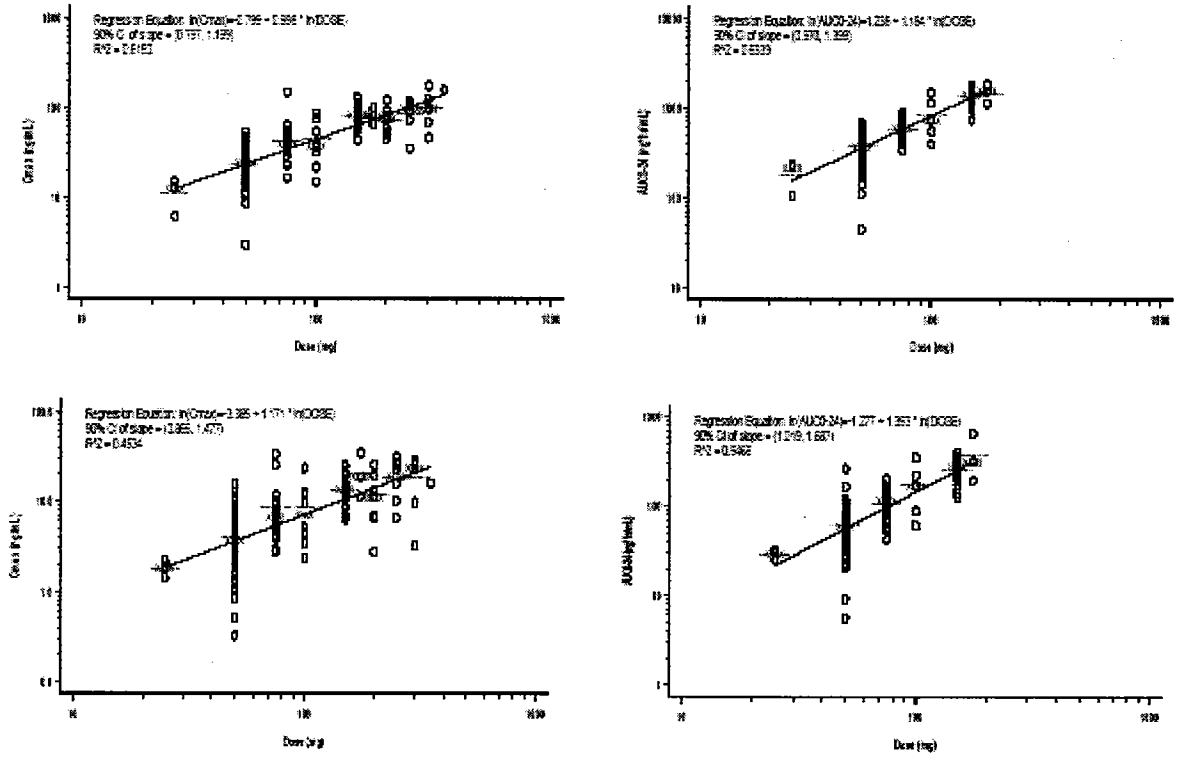


Figure 18: Log-Log plots of Cmax vs. dose and AUC vs. dose for sunitinib (upper panel) and SU012662 (lower panel) following single doses of sunitinib. (Symbols: observed values, Line: best-fitting regression line).

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The degree of accumulation of sunitinib, SU012662, and total drug (sunitinib + SU012662) within a single dosing cycle (Cycle 1), and between dosing cycles (Cycle >1 to Cycle 1), was evaluated in Studies 248-ONC-0511-002, RTKC-0511-005, RTKC-0511-013, and RTKC-0511-016.

Within-cycle intra-patient accumulation ratios for C_{max} and AUC_{0-24} (Day 28/Day 1 and Day 28/Day 14 for Schedule 4/2, and Day 14/Day 1 for Schedule 2/2 and 2/1) following QD dosing for 14 days (Schedule 2/2 and 2/1) or for 28 days (Schedule 4/2) are summarized in the table below. Accumulation per cycle was approximately 3- to 4-fold for sunitinib and 3.5- to 4.5-fold for total drug (sunitinib + SU012662) with repeat dosing, and was independent of dosing schedule (i.e., 14- or 28-day dosing).

For the 50-mg QD dose groups mean intra-patient accumulation ratios for C_{max} and AUC_{0-24} of sunitinib, SU012662, and total drug (Cycle 2/Cycle 1) were equal to or close to 1 for all schedules. Though patient numbers were small, similar results were also observed for Cycle 3/Cycle 1 intra-patient ratios.

These results demonstrate that no significant additional accumulation occurred in cycles >1 for any of the dosing schedules tested. Additionally, the similarity of sunitinib and SU012662 exposures (C_{max} and AUC_{0-24}) between Days 14 and 28 in Cycle 1 and between cycles (Cycles >1 to Cycle 1) demonstrate that no auto-induction of sunitinib and/or SU012662 metabolism occurs with repeat dosing of sunitinib.

Table 13: Summary of intrapatient AUC(0-24) and Cmax ratios (cycle to cycle) for sunitinib, SU012662 and total drug (sunitinib+SU012662) following different schedules of 50mg QD dosing.

Parameter	Intrapatient Ratios (Cycle 2/Cycle 1)[a] Geometric Mean (95% CI)			Cycle 2/Cycle 1 Geometric LS Mean Ratio (90% CI)[b]		
	Schedule 2/1 (n = 10)	Schedule 2/2 (n = 16)	Schedule 4/2 (n = 9)	Schedule 2/1 (n = 10)	Schedule 2/2 (n = 18)	Schedule 4/2 (n = 11)
Sunitinib						
C_{max}	0.86 (0.68, 1.10)	0.91 (0.75, 1.10)	1.16 (0.83, 1.61)	0.83 (0.69, 1.01)	0.91 (0.78, 1.06)	1.04 (0.76, 1.44)
AUC_{0-24}	0.93 (0.73, 1.18)	0.91 (0.74, 1.11)	1.25 (0.86, 1.75)	0.90 (0.75, 1.08)	0.91 (0.77, 1.07)	1.16 (0.81, 1.65)
SU012662						
C_{max}	1.03 (0.75, 1.42)	0.93 (0.79, 1.10)	0.92 (0.65, 1.26)	0.96 (0.75, 1.22)	0.93 (0.81, 1.06)	0.94 (0.74, 1.20)
AUC_{0-24}	1.06 (0.77, 1.47)	0.91 (0.77, 1.09)	1.15 (0.86, 1.54)	1.00 (0.78, 1.28)	0.91 (0.79, 1.05)	1.12 (0.91, 1.39)
Total Drug						
C_{max}	0.90 (0.69, 1.17)	0.92 (0.78, 1.09)	1.08 (0.79, 1.49)	0.86 (0.70, 1.06)	0.92 (0.80, 1.05)	1.08 (0.84, 1.38)
AUC_{0-24}	0.96 (0.74, 1.24)	0.92 (0.76, 1.10)	1.16 (0.82, 1.64)	0.92 (0.76, 1.13)	0.91 (0.79, 1.06)	1.17 (0.90, 1.51)

Source: Appendix 2, Tables A-3.2.1.1 to A-3.2.1.3, A-3.2.2.1 to A-3.2.2.3, and A-3.2.3.1 to A-3.2.3.3, and ad-hoc Tables 5 to 7.
ANOVA = Analysis of Variance. AUC_{0-24} = Area Under the Plasma Concentration Time Curve From 0 to 24 Hours; C_{max} = Maximum Concentration; CI = Confidence Interval; Geom. LS Mean = Geometric Least Squares Mean; PK = Pharmacokinetic.
Note: All data presented are for the 50-mg dose groups.

[a] Ratios are PK parameter ratios of the last dosing day in Cycle 2 to the last dosing day in Cycle 1.

[b] Results from repeated measures ANOVAs comparing PK parameters (last dosing day in Cycle 2 to last dosing day in Cycle 1), with a fixed effect for cycle, and subjects as the experimental units.

Table 14: Summary of intra-patient AUC(0-24) and Cmax ratios (multiple/single dose) for sunitinib, SU012662 and total drug (sunitinib+SU012662) following different schedules of 50mg QD dosing.

Parameter	Intrapatient Ratios Geometric Mean (95% CI)			Geometric LS Mean Ratio[a] (90% CI)	
	Schedule 2/1 Day 14/Day 1 (n = 17)	Schedule 2/2 Day 14/Day 1 (n = 19)	Schedule 4/2 Day 28/Day 1 (n = 23)	Schedules 4/2, 2/2, and 2/1 Day 14/ Day 1 n = 52	Schedule 4/2 Day 28/Day 1 n = 23
Sunitinib					
C_{max}	3.88 (3.10, 4.85)	3.10 (2.42, 3.97)	2.84 (2.26, 3.56)	3.34 (3.00, 3.72)	2.83 (2.37, 3.38)
AUC_{0-24}	4.25[b] (3.59, 5.04)	3.61 (2.91, 4.47)	3.55 (2.89, 4.37)	3.89 (3.54, 4.28)	3.50 (2.97, 4.11)
SU012662					
C_{max}	8.22 (6.52, 10.4)	6.73 (4.35, 10.4)	8.27 (6.39, 10.7)	7.38 (6.29, 8.65)	8.26 (6.71, 10.2)
AUC_{0-24}	10.0[c] (8.37, 12.0)	8.48 (6.22, 11.6)	10.2[d] (8.12, 12.9)	8.97 (7.91, 10.2)	10.0 (8.30, 12.1)
Total Drug					
C_{max}	4.42 (3.56, 5.50)	3.59 (2.73, 4.71)	3.57 (2.86, 4.46)	3.89 (3.48, 4.34)	3.57 (3.00, 4.24)
AUC_{0-24}	4.93[b] (4.18, 5.80)	4.29 (3.45, 5.33)	4.48 (3.64, 5.50)	4.60 (4.20, 5.04)	4.41 (3.75, 5.19)

Source: Appendix 2, Tables A-3.2.1.1 to A-3.2.1.3, A-3.2.2.1 to A-3.2.2.3, and A-3.2.3.1 to A-3.2.3.3, and ad-hoc Tables 3 and 4.
ANOVA = Analysis of Variance; AUC_{0-24} = Area Under the Plasma Concentration Time Curve From 0 to 24 Hours; C_{max} = Maximum Concentration; CI = Confidence Interval; Geom. LS Mean = Geometric Least Squares Mean; PK = Pharmacokinetic.
Note: All data presented are from Cycle 1.
[a] Results from repeated measures ANOVAs comparing PK parameters (multiple-dose to single-dose) for the 50 mg dose groups, with a fixed effect for study day, and subjects as the experimental units.
[b] N=16.
[c] N=15.
[d] N=21.

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.

The applicant has used population PK modeling approaches using NONMEM to not only describe sunitinib and SU012662 PK following single and multiple dose administration of sunitinib, but also to identify covariates that are important determinants of sunitinib and SU012662 disposition. These covariates included body weight, race, gender, tumor type, age, ALT, CLcr, and Performance Status (ECOG score or KPS converted to an ECOG score).

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?

Population PK modeling approach, using NONMEM, was performed to: 1) Describe sunitinib and SU012662 PK following single and multiple dose administration of sunitinib; and 2) Identify covariates that are important determinants of sunitinib and SU012662 disposition, including weight, race, gender, tumor type, age, ALT, CLcr, and Performance Status (ECOG score or KPS converted to an ECOG score).

The analyzed dataset included sunitinib and SU012662 concentrations collected in subjects from 13 clinical studies at timed intervals following both single and multiple dose regimens in healthy subjects and oncology patients.

The plasma concentration versus time data of sunitinib and SU012662 could not be modeled simultaneously and were therefore modeled separately. Sunitinib PK was modeled using a 2-compartment oral model. The CL/F of sunitinib was estimated at 37.6 L/hr. The Vd/F was estimated to be 2230 L. Inter-individual variability was estimated at 40% and 36% respectively.
T1/2 was estimated to be approximately 41 hours (95% CI, 35-48 hours) with high inter-individual variability (57% CV). Absorption rate was estimated at 1.07/hr, suggesting a 0.6 hour absorption T1/2. SU012662 was also modeled using a 2-compartment model. Based upon pre-clinical observations, parent to metabolite conversion of 21% was assumed to bring the magnitude of the parameters into a more physiologically relevant level. CL/F was estimated at 20.5 L/hr. Vd/F was estimated to be 3260 L. Inter-individual variability on these terms was estimated at 46% and 53%, respectively for CL/F and Vd/F. T1/2 was approximately 110 hours (95% CI 91-133 hours) with high inter-individual variability (79% CV). Absorption and formation rate was 1.00/hr, suggesting a 0.7 hour half-life for formation.

Gender and tumor type were significant covariates in the covariate model for CL/F for sunitinib. Weight, age, gender and tumor type were significant covariates for Vd/F for sunitinib. Weight, gender and tumor type were significant covariates for CL/F for SU012662, while weight, age, gender and tumor type were significant covariates for Vd/F for SU012662. The role of specific intrinsic factors is discussed below. The impact of any differences due to these intrinsic factors on the E-R relationship and need for dosing adjustments in discussed in the next section.

Gender: The dataset used for population PK analysis included 400 males and 196 females. Females displayed a 35% decrease in CL/F of sunitinib and a 37% decrease in

CL/F of SU012662, relative to males. These differences translate to an approximately 50% higher total (sunitinib + SU012662) drug AUC, compared to males.
The precise mechanism for this gender difference in clearance is unknown. There are a few reports in the literature on gender differences in CYP3A4 activity, but those studies suggest females have higher clearances than males, which is the opposite of the current finding. To verify that this gender difference is not due to an increased use of CYP3A4 inhibitors by females in the studies, the concomitant medications used by the patients in the studies were surveyed. While there was sporadic use of CYP3A4 inhibitors (e.g., 3 GIST females received fluconazole for 1-6 days), there was no pattern suggesting that the increased clearance seen in females was due to concomitant use of CYP3A4 inhibitors.

Body weight: The dataset used for population PK analysis included body weight from 34 to 168 kg. Weight was positively correlated with Vd/F of sunitinib and CL/F and Vd/F of SU012662. Relative to an individual of 75 kg, a 40 kg individual may have a 22% decrease in Vd/F of sunitinib and a 28% and 39% decrease in CL/F and Vd/F of SU012662, respectively. These differences translate to a less than 5% increase in combined steady-state AUC (due to decreased CL/F of SU012662 only). Alternatively, for an individual of higher weight (100 kg), Vd/F of sunitinib may increase 12%, CL/F of SU012662 may increase 25% and Vd/F of SU012662 may increase 16% compared to an individual weighing 75 kg. These differences translate to a less than 5% decrease in combined AUC, and would not be expected to impact the response to sunitinib.

Race: The population PK dataset included 519 White, 16 Blacks 47 Asians (including Japanese and Pacific Islanders) and 14 patient classified as "other". The effect of race thus could not be adequately evaluated in this study.

Age: The dataset used for population PK analysis included ages ranging from 18 to 84 years (85 subjects < 40 years; 118 subjects 40 to < 60 years; 65 subjects 60-75 years, 10 subjects > 75 years). There is no age effect on CL/F of both sunitinib and SU012662. Therefore, AUC will not be affected by age. Although age was positively correlated with Vd/F, the impact of age on C_{max} was minimal. For an individual of 25 years Vd/F may decrease 8% and 17% for sunitinib and SU012662, respectively relative to an individual of 50 years. Alternatively for an elderly individual of 75 years, Vd/F may increase 5% and 11% for sunitinib and SU012662, respectively. These differences would not be expected to affect the response.

Tumor Type: The dataset for population PK analysis included 73 healthy subjects, 229 patients with GIST, 158 patients with MRCC, 107 patients with solid tumors, and 29 patients with AML. There was an effect of tumor type on CL/F for both sunitinib and SU012662. The fixed effects for the different tumor types indicated a 6% decrease in CL/F of sunitinib for GIST patients and a 10% decrease in CL/F of sunitinib for MRCC patients, relative to healthy subjects. Vd/F of sunitinib showed a 23% decrease in GIST patients and a 58% increase in MRCC patients compared to healthy subjects. CL/F of SU012662 showed a 16% decrease in GIST patients and a 47% decrease in MRCC patients. These differences would translate to a 8% lower AUC in GIST patients

compared to healthy controls and a 15% lower AUC in MRCC patients compared to healthy controls.

Hepatic Impairment: The effect of hepatic impairment on sunitinib and SU012662 PK has not been evaluated. The applicant did explore the effect of AST, as a marker of hepatic impairment, on the PK of sunitinib and SU012662 as part of the population PK analysis, but found no significant effect. However, since AST is not the best marker of hepatic impairment, the result is inconclusive. In any case, given that both sunitinib and SU012662 are eliminated by the hepatic route, the sponsor is currently conducting a study evaluating the effect of different degrees of hepatic impairment on the PK of sunitinib and SU012662.

Renal Impairment: The applicant did explore the effect of creatinine clearance (CLcr) on the clearance of sunitinib and SU012662 as part of the population PK analysis. There were no significant findings, although it must be noted that the sample consisted mostly of individuals with normal or mildly impaired renal function (CLcr> 50 ml/min). There were very few individuals with moderate renal impairment (CLcr between 30-50 ml/min), and none with severe renal impairment (CLcr<30 ml/min). The following figure shows the relationship between CLcr and AUC (from base model individual CL estimates) in the population PK sample.

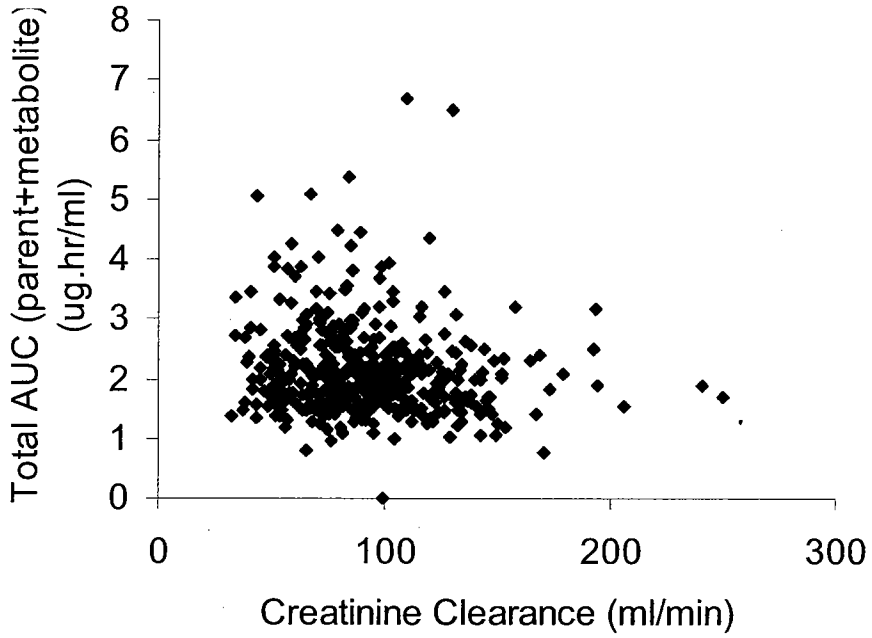


Figure 19: Total AUC (parent+metabolite) vs. creatinine clearance in patients included in population analysis. The plot illustrates the lack of relationship between renal function and exposure in the patients evaluated.

Thus, renal impairment is not expected to have a major impact on the PK of sunitinib or SU012662, given that <20% of the total drug is eliminated renally. However, the

sponsor is planning to conduct a study to evaluate the PK of sunitinib and SU012662 in patients with severe renal impairment and end-stage renal disease patients on dialysis.

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

No dosing adjustments necessary.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

[ ]

2.3.2.3 Gender

Kaplan-Meier curves for TTP (investigator-assessed, across both GIST studies) showed slower progression for females (red in figure below) than for males (black in figure below) receiving 50 mg sunitinib. The same trend is not seen in placebo patients. [note: X-axis scales are different]
Rates of progression (RR for Progression based on RECIST) also showed a trend toward lower values for females compared to males, in the active treatment group (quartiles).

Table 15: Number (and %) of patients showing tumor progression, classified into placebo and active groups, and further sub-classified based on total AUC quartiles.

GROUP	**Males Counts (%)**	**Females Counts (%)**
Placebo	26/63 (41.3%)	15/38 (39.5%)
Sunitinib	18/145 (12.4%)	6/80 (7.5%)
GROUP	**Males**	**Females**
Placebo	26/63 (41.3%)	15/38 (39.5%)
AUCtot Quartile 1	3/44 (6.8%)	0/12 (0.0%)
AUCtot Quartile 2	6/37 (16.2%)	1/19 (5.2%)
AUCtot Quartile 3	4/37 (10.8%)	1/19 (5.2%)
AUCtot Quartile 4	5/27 (18.5%)	4/30 (13.3%)

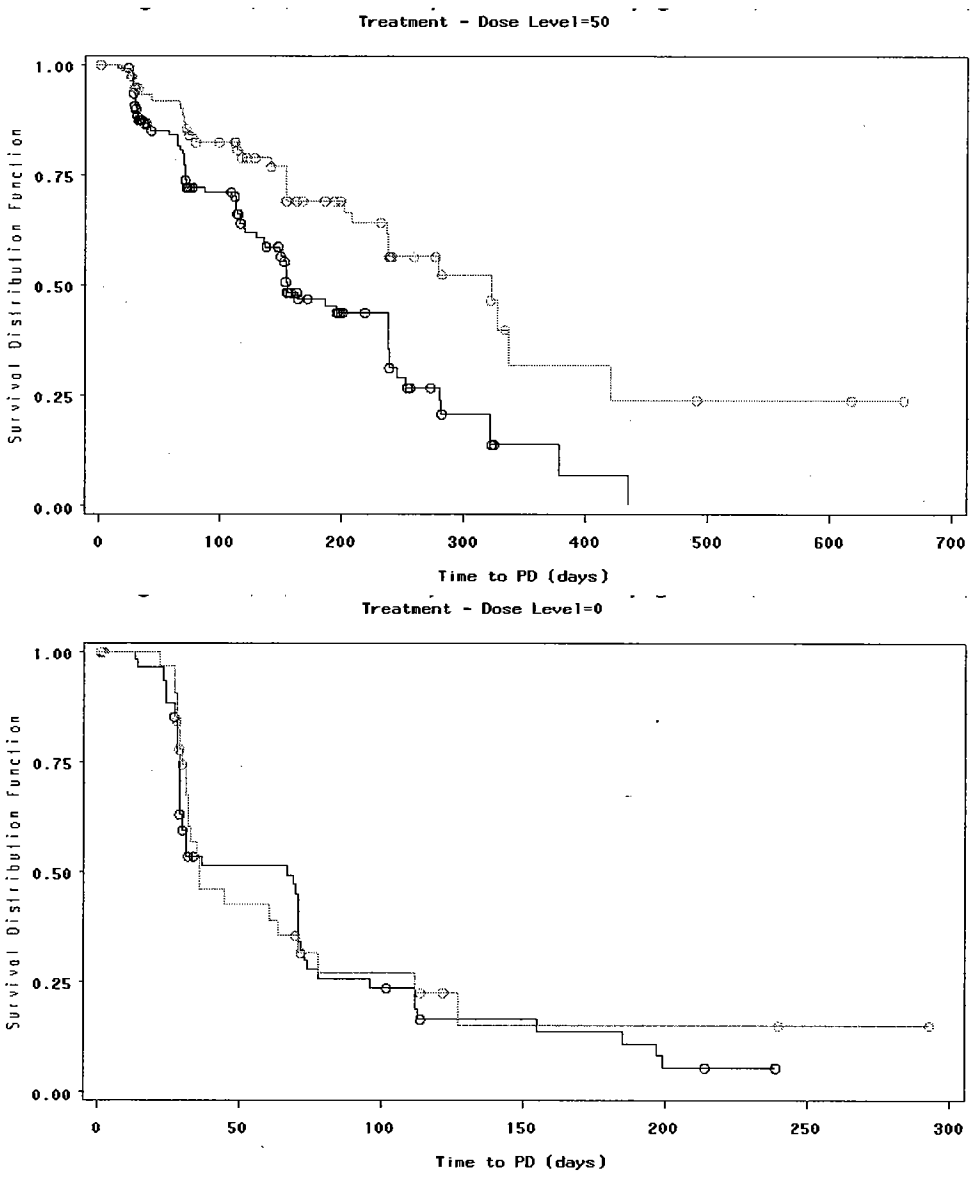


Figure 20: Kaplan-Meier curves for time to tumor progression, for sunitinib (upper panel) and placebo (lower panel), by gender (red: females, black: males), in GIST patients in studies 13 and 1004.

Could this apparent difference be due to gender differences in PK or gender differences in PD (sensitivity) or both?

Gender differences in PK:

Analysis indicates an apparent gender difference in sunitinib and active metabolite clearances.

a) Non-compartmental PK parameters from two phase 2 studies (002 and 005) in which doses of 25 to 100 mg of sunitinib were administered to male and female solid tumor patients were examined for gender differences. The following table shows the mean

apparent clearance of sunitinib and dose-normalized AUC of parent and metabolite in males and females from these studies (clearance of metabolite was not determined).

	Males (n=37) Mean (SD)	Females (n=32) Mean (SD)
CL/F for Sunitnib [L/hr]	66.3 (28.8)	51.0 (29.2)
Dose-normalized AUCinf for Sunitinib [(ng.hr/ml]/mg]	20.9 (17.6)	27.8 (15.5)
Dose-normalized AUCinf for SU012662 [(ng.hr/ml]/mg]	8.3 (21.1)	8.8 (8.7)
Dose-normalized AUCinf of total(Sunitnib+SU012662) [(ng.hr/ml]/mg]	28.7 (30.6)	34.6 (15.6)

There was large variability in AUCs across individuals. Females showed a 33% higher AUC for sunitinib compared to males, and 6% higher AUC for the metabolite compared to males.

b) Population PK models showed a significant effect of gender on the clearance of sunitinib and its active metabolite. Based on the covariate models, typical clearances in male and female GIST patients were estimated and from these, AUCs for the 50 mg dose was calculated.

	AUC(parent)	AUC(metabolite)	AUC(total)
Males	1.46 µg.hr/ml	0.5 µg.hr/ml	1.96 µg.hr/ml
Females	2.25 µg.hr/ml	0.8 µg.hr/ml	3.05 µg.hr/ml

Comparison of the total AUC (parent+metabolite) indicated that females had a 50% higher exposure than males.
The higher exposure in females could partially explain the apparent gender difference in TTP.

Gender differences in PK-PD:
Cox proportional hazards analysis of TTP showed a significant negative effect of AUC, i.e., a decrease in risk of progression with increase in AUC. The hazard ratio was 0.5 indicating a 50% decrease in risk of progression for each unit increase in AUC [average AUC for 50 mg dose is ~1.8 ug.hr/ml]

Given this exposure-TTP relationship, we wanted to determine if there was an effect of gender on TTP, after accounting for the effect of exposure.

Results: Cox proportional hazards analysis:

Model	**Independent Variable**	**Coefficient**	**p-value**	**Hazard Ratio**
I	AUCtotmean	-0.668	<0.0001	0.513
II	AUCtotmean	-0.637	<0.0001	0.529
	Sex	-0.331	0.2137	0.718
	AUCtotmeanXSex	-0.050	0.7864	0.951

Results from Model II indicate that there is no significant main effect of sex or significant interaction between AUC and sex in the relationship with TTP.
As the observed proportion of females and males showing progression was similar in the placebo group (see figure 20), and appeared to differ under active drug, we wanted to evaluate the effect of sex on the steepness (or slope) of the exposure-TTP relationship. Operationally, this is the same as looking at the AUCxSEX interaction without looking at the main effect of SEX in the regression analysis (Model III).

Model	Independent Variable	Coefficient	p-value	Hazard Ratio
III	AUCtotmean	-0.573	<0.0001	0.564
	AUCtotmeanXSex	-0.229	0.0454	0.795

The above results indicate a significant effect of sex on the exposure-TTP relationship. Due to the significant interaction, the relative risk of progression for males and for females will depend on the AUC, and can be calculated as [exp(b1+b2*sex)]. So, for AUC=1, the relative risk for progression in males can be estimated as 0.56 [exp(-0.573-0.229*0)] and for females as 0.45 [exp(-0.573-0.229*1)]. Similarly, the relative risk of progression can be calculated at the typical AUC (1.75 ug.hr/ml) for the 50 mg sunitinib dose. The relative risk at this AUC is 0.367 for males and 0.246 for females.
The hazard ratio of 0.795 reported in the table above is the ratio of the hazard ratios for females to males when AUC=1, therefore must be interpreted with caution at other values of AUC.

The following figure shows the calculated relative risk of progression as a function of AUC for males and females based on Model III.

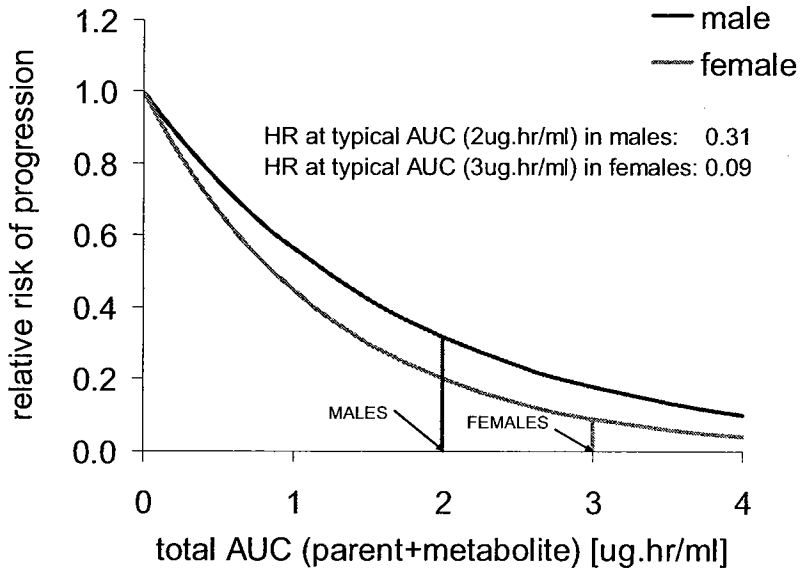


Figure 21: Relative risk of tumor progression vs. total AUC (sunitinib+SU012662) in GIST males and GIST females, based on Cox PHM.

In conclusion, females have a 50% higher exposure (sunitinib + metabolite) compared to males. Exposure-toxicity analysis has demonstrated a lack of gender differences. Females also have a somewhat slower time to progression compared to males.

These preliminary results are based on the analysis of investigator assessments of tumor progression, and will need to be confirmed using the core-lab independent assessments of tumor progression (which were only done for study 1004), prior to determining the need for any dosing adjustments based on gender.

2.3.2.4 Race

The majority of patients in the studies were White with very small numbers of Blacks (n=16) and Asians (n=47) in the GIST, MRCC and solid tumor studies. The numbers of individuals in each of these groups were too small for any meaningful interpretation of these results. This suggests the need to continue to collect data in ongoing and future studies, along with covariate information, to further refine the model and better describe the effect of race and other covariates on the PK of sunitinib and SU012662.

2.3.2.5 Renal impairment

Given that <20% of a dose of sunitinib is eliminated renally (majority of parent drug and active metabolite are eliminated in feces), adjustments for renal impairment do not appear necessary. The sponsor is planning to conduct a study to evaluate the PK of sunitinib and its metabolite in patients with severe renal impairment and end-stage renal disease patients on dialysis. Any dosing adjustments in these severely impaired patients or patients on dialysis will be addressed following the completion of this study.

2.3.2.6 Hepatic impairment

The effect of hepatic impairment on sunitinib and SU012662 PK has not been evaluated. Given that both sunitinib and SU012662 are eliminated by the hepatic route, the sponsor is currently conducting a study evaluating the effect of different degrees of hepatic impairment on the PK of sunitinib and SU012662.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Animal studies have shown that sunitinib and its metabolites are excreted in rat milk. However, no studies have been conducted in humans to determine if sunitinib or SU012662 are excreted in human milk. The label includes a precaution for nursing mothers to avoid breastfeeding while on sunitinib.

2.3.2.8 What pharmacogenetics information is there in the application and is it important or not?

The sponsor has collected tumor biopsy samples for analysis of mutations/genotypes of the target RTK genes (KIT, PDGFR, VEGFR etc.) as well as for expression and

activation of KIT, PDGFR and VEGFR receptors in several of their studies. However, no results have been included in the study reports.

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

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Both sunitinib and its major active metabolite, SU012662 are substrate of CYP3A4, thus, there is potential for drug-drug interactions when sunitinib is co-administered with inhibitors and inducers of this CYP enzyme.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

In vitro human liver microsomal studies indicate that the primary cytochrome P450 (CYP) enzyme involved in the N-deethylation of sunitinib to its major active metabolite, SU012662 is CYP3A4. CYP2B6, 2C8, 2C9, and 2C19 contribute little to the N-deethylation of sunitinib (Study SU011248-PDM-051). The N-deethylation of sunitinib to SU012662 represents the major pathway of sunitinib metabolism. The kinetic constants, K_m and V_{max} for sunitinib N-deethylation by human hepatic microsomes are 73.21 pM and 4.28 pmol/mg/min, respectively.

Table 16: Effect of various inhibitors on the N-Deesthylation of SU011248 (48 µM)

CYP Enzyme	Inhibitor	Concentrations (µM)	*Percent of Control Sunitinib Remaining
1A2	Furafylline	0, 10, and 20	100%
2A6	Coumarin	0, 1, 5, and 50	100%
2B6	7-Ethoxy-4-trifluoro methyl coumarin	0, 1, 5, and 10	60%
2C8	Quercetin	0, 1, 5, and 10	75%
2C9	Sulfaphenazole	0, 1, 5, and 10	75%
2C19	S-Mephenytoin	0, 35, 50, and 100	75%
2D6	Quinidine	0, 0.1, 0.5, 5, and 10	100

2E1	4-Methypyrazole	0, 1, 5, and 10	100
3A4	Ketoconazole	0, 0.125, 0.625, 1.25, 2.5	2.0%
3A4	TAO	0, 12.5, 25, 50, and 100	20%

*at the highest concentration

In vitro human liver microsomal studies also indicate that the primary CYP enzyme involved in the metabolism of deethylated metabolite, SU012662 is CYP3A4 (7% of control) (SU011248-PDM-050). CYP1A2 may have a minor role in the metabolism of this compound (>75% of control), while 2D6, 2C9, and 2C19 do not appear involved (100% of control). SU012662 is metabolized to form an amine metabolite, SU014335. The formation of SU012662 from sunitinib is faster than the formation of SU014335 from SU012662. The V_{max} for the deethylation of sunitinib to SU012662 by human liver microsomes is 9-fold higher than the dealkylation of SU012662 to SU014335 (2373 pmol/mg/min versus 264 pmol/mg/ min, respectively).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Inhibition

In vitro studies with human liver microsomes indicate that neither sunitinib nor SU012662 is likely to inhibit metabolic clearance of drugs that are substrates for CYP450 enzymes at clinically relevant concentrations (Study SU011248-PDM-053).

Table 17: Evaluation of Sunitinib as an Inhibitor of Human CYP450 Enzymes*

CYP Enzyme	Activity	Substrate Concentration (μM)	Ki (μM)	#[I]/ki
1A2	7-Ethoxyresorufin O-dealkylase	0.25	5.4±0.5	0.037
2A6	Coumarin 7-hydroxlase	0.5	140±40	0.001
2B6	S-Mephenytoin N-demethylase	1500	>150	NA
2C8	Paclitaxel 6α –hydroxylase	15	28±5	0.007
2C9	Diclofenac 4'-hydroxylase	4.0	>150	NA
2C19	S-Mephenytoin 4'-hydroxylase	35	110±20	0.002
2D6	Dextromethorphan O-demethylase	5.0	24±2	0.008
2E1	Chlorzoxazone 6-hydroxylase	30	>150	NA
3A4/5	Midazolam 1'-hydroxylase	3.0	>150	NA
3A4/5	Testosterone 6β –hydroxylase	100	54±6	0.004
4A9/11	Lauric acid 12-hydroxylase	7.5	>150	NA

*[25 μM except for CYP1A2 activity, it was 10 μM]
#[[I]=plasma C_{max} of 0.2 μM (72.2 ng/mL) after 50 mg QD to 9 patients, Study 248-ONC-0511-002]

Table 18: Evaluation of SU012662 as an Inhibitor of Human CYP450 Enzymes*

CYP Enzyme	Activity	Substrate Concentration (μM)	ki (μM)	#[I]/ki
1A2	7-Ethoxyresorufin O-dealkylase	0.25	5.8±0.4	0.0172
2A6	Coumarin 7-hydroxlase	0.5	140±30	0.0007
2B6	S-Mephenytoin N-demethylase	1500	>150	NA
2C8	Paclitaxel 6α –hydroxylase	15	52±8	0.001
2C9	Diclofenac 4'-hydroxylase	4.0	79±10	0.0013
2C19	S-Mephenytoin 4'-hydroxylase	35	78±21	0.0013
2D6	Dextromethorphan O-demethylase	5.0	18±2	0.0055
2E1	Chlorzoxazone 6-hydroxylase	30	>150	NA
3A4/5	Midazolam 1'-hydroxylase	3.0	>150	NA
3A4/5	Testosterone 6β –hydroxylase	100	69±8	0.0015
4A9/11	Lauric acid 12-hydroxylase	7.5	>150	NA

*[25 μM except for CYP1A2, 2C8, and 2D6 activities, it was 1.0, 10, and 10 μM, respectively]
#[[I]=plasma C_{max} of 0.1 μM (33.7 ng/mL) after 50 mg QD of sunitinib to 9 patients, Study 248-ONC-0511-002]

The results indicate that sunitinib and SU012662 are unlikely to cause clinically relevant drug-drug interactions through inhibition of clearance of drugs that are metabolized by CYP450 enzymes ([I]/ki < 0.02), according to our draft Guidance for Industry on Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling (http://www.fda. gov/cder/ guidance/2635fnl.pdf)).

In a separate *in vitro* study with human liver microsomes (Study SU011248-PDM-052), the inhibitory effect of sunitinib and SU012662 on the CYP3A4-mediated 1'-hydroxylation of midazolam (3 μM) was examined. The estimated apparent k_i values for sunitinib on 1'-hydroxylation of midazolam ranges from 9.5-28 μM, while that for SU012662 is > 100 μM). The estimated [I]/k_i ratio for sunitinib ranges from 0.01-0.021; suggesting a little inhibitory effect for sunitinib on the CYP3A4-mediated 1'-hydroxylation of midazolam. SU012662 has no inhibitory effect on the CYP3A4-mediated 1'-hydroxylation of midazolam.

Induction

In vitro studies in cultured human hepatocytes suggest that neither sunitinib nor SU012662 is likely to induce metabolic clearance of drugs that are substrates for CYP1A2, 2E1, and 3A4 enzymes at clinically relevant concentrations (Study SU011248-PDM-009).

Table 19: Effects of Treating Cultured Human Hepatocytes with Sunitinib, SU012662, or Probe Inducers on Microsomal Cytochrome P450 Enzyme Activities

Treatment	*In vitro* Concentration	Enzymatic Activity (pmol/mg microsomal protein/min)		
		7-Ethoxyresorufin *O*-dealkylation	Chlorzoxazone 6-hydroxylation	Testosterone 6b-hydroxylation
		(CYP1A2)	(CYP2E1)	(CYP3A4/5)
*DMSO	(0.1% v/v)	7.9 ± 1.2	618 ± 253	3390 ± 660
#Saline	(0.1% v/v)	7.2 ± 1.5	240 ± 164	2610 ± 1330
SU011248	0.25 µM	8.0 ± 1.5	567 ± 254	3520 ± 1430
SU011248	2.5 µM	9.4 ± 0.6	568 ± 143	3230 ± 930
SU011248	10 µM	8.8 ± 2.1	445 ± 290	1290 ± 1020
SU011248	25 µM	9.7	ND	ND
SU012662	0.25 µM	9.1 ± 2.1	584 ± 331	3620 ± 1590
SU012662	2.5 µM	12 ± 1.3	540 ± 330	2940 ± 1200
SU012662	10 µM	16.2 ± 0.3	462 ± 328	1590 ± 840
SU012662	25 µM	9.5	156	82.7
β-Naphtho-flavone	33 µM	74 ± 52.5	668 ± 404	2010 ± 1840
Isoniazid	100 µM	5.8 ± 1.4	382 ± 252	1730 ± 1270
Rifampin	20 µM	14.9 ± 3.8	861 ± 192	11600 ± 500

*DMSO= Dimethyl sulfoxide was the solvent for all compounds except isoniazid
#Saline was the solvent for isoniazid
ND=Not determined

ß-naphthoflavone is the major inducer of CYP1A2-mediated 7-ethoxy-resorufin *O*-dealkylation (EROD) activity, which is increased by 9.25-fold in the presence of 33 µM ß-naphthoflavone. Sunitinib (0.25, 2.5, or 10 µM) has little or no effect on EROD 1A2-mediated activity. In contrast, SU012662 caused a concentration-dependent increase in EROD CYP1A2 activity (up to 2.1-fold at 10 µM). Rifampin increased the EROD 1A2-mediated activity by 1.9-fold.

Isoniazid is the major inducer of CYP2E1-mediated chlorzoxazone 6-hydroxylation activity, which is increased by 1.6-fold in the presence of 100 µM isoniazid. Sunitinib and SU012662 appear to cause a concentration-dependent decrease in the chlorzoxazone 6-hydroxylation 2E1-mediated activity (up to 25-28% at 10 µM). Rifampin increased the chlorzoxazone 6-hydroxylation CYP2E1-mediated by 1.4-fold. This decrease in 2E1 activity may be attributed to a generalized toxicity caused by the test compounds, especially at the higher concentrations.

Rifampin is the major inducer of CYP3A4/5-mediated testosterone 6β-hydroxylation activity, which is increased by 3.4-fold in the presence of 20 μM rifampin.

Sunitinib or SU012662 had a little effect on the 3A4/5-mediated testosterone 6β-hydroxylation activity at the 0.25 and 2.5 μM concentrations for both compounds. At The 10 μM concentration for both compounds, a 53-62% decrease in CYP3A4/5 activity is observed.This decrease in activity may be attributed to generalized toxicity, as was observed with chlorzoxazone 6-hydroxylation activity.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The potential of sunitinib and SU012662 as substrates for efflux transporters, P-glycoprotein (P-gp) was examined using Caco-2 cells in Study SU011248-PDM-092. The permeability of SU011248 was investigated with Caco-2 cell lines. The results indicate the permeability of SU011248 was 2.20 x 10^{-6} cm/sec and 3.81 x 10^{-6} cm/sec at concentrations of 1 and 10 μM, respectively. The evaluation of SU012662, the metabolite of SU011248, revealed low permeability with Papp A>B values of 1.05 x 10^{-6} and 0.77 x 10^{-6} cm/sec (Table 4) at concentrations of 1 and 10 μM,
Sunitinib and SU012662 exhibited moderate and significant P-gp mediated efflux, respectively. The efflux of sunitinib was inhibited by 69% and 40% in the presence of verapamil and vinblastine, respectively (see table below). The efflux of SU012662 was inhibited by 92% and 82% in the presence of verapamil and vinblastine, respectively (see table below). Although both verapamil and vinblastine decreased the efflux ratio for sunitinib and SU012662, this ratio did not approach unity, suggesting that other transporters may be involved in the efflux of these compounds besides P-gp.

Table 20: Evaluation of SU011248 as a Substrate of P-glycoprotein in Caco-2 Cells

	Concentration	Efflux Ratio	% Inhibition
Compound	**(μM)**		
SU011248	1.0	9.3	--
SU011248 + Verapamil	1.0	2.9	69
SU011248 + Vinblastine	1.0	5.5	40

Table 21: Evaluation of SU012662 as a Substrate of P-glycoprotein in Caco-2 Cells

	Concentration	Efflux Ratio	% Inhibition
Compound	**(μM)**		
SU012662	1.0	366.3	--
SU012662 + Verapamil	1.0	29.9	91.8
SU012662 + Vinblastine	1.0	66.9	81.7

The potential for sunitinib to inhibit P-gp was evaluated in Study SU011248-PDM-071. Sunitinib does not appear to inhibit P-gp-mediated transport of Rhodamine 123 in HCT-8 human intestinal epithelial cells, with an IC_{50} of 39 μM compared to an IC_{50} of 0.7 μM for Cyclosporin A. SU012662 has not been tested in this study

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The potential of sunitinib and SU012662 as substrates for breast cancer resistance protein (BCRP) was examined using Caco-2 cells in Study SU011248-PDM-092. Sunitinib may not be a substrate for the breast cancer resistant protein (BCRP) transporter. At clinically relevant concentrations (0.2 μM), this transporter are not expected to affect the pharmacokinetics of sunitinib. SU012662 is a substrate of BCRP. SU012662 showed efflux by BCRP at clinically relevant concentrations (0.1 μM), suggesting that the elimination of SU012662 may be facilitated in the liver and kidney by BCRP transporter.

Table 22: Role of BCRP in the Efflux of sunitinib.

Concentration (μM)	BCRP Efflux Ratio
0.2	NE
0.5	NE
1.0	NE
2.0	1.8
5.0	1.9
10.0	NE

NE=Not evaluated

Table 23: Role of BCRP in the Efflux of SU012662.

Concentration (μM)	BCRP Efflux Ratio
1.0	4.1
2.0	3.9
5.0	3.7

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

None, sunitinib is to be administered as a **single agent** for the treatment of patients with gastrointestinal stromal tumor (GIST) and for the treatment of patients with metastatic renal cell carcinoma (MRCC).

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The most frequent co-medications that were administered with sunitinib during the pivotal Phase 3 Study A6181004 for the GIST indication were Tylenol (21%), Allopurinol (15.8%), Colace (15.8%), Oxycontin (15.8%), Penicillin (15.8%), Oxycodone (10.5%), Multivitamins (10.5), Zofran (10.5%), and Pepcid (10.5%).

The most frequent co-medications that were administered with sunitinib during the pivotal Phase 2 Study A6181006 for the MRCC indication were Tylenol (37%), Multivitamins (25%), Colace (22%), Compazine (21%), Pepcid (20%), Oxyocet (19%), oxycodone (19%), Imodium (19%), Ativan (17%), oxycontin (17%), ibuprofen (16%), Pantoprazole (16%), Norvasc (14%), Prevacid (14%), diphenhydramine (14%), and Zofran (14%).

The potential for drug-drug interactions between the above supportive care co-medications and sunitinib is unlikely.

2.4.2.8 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Coadministration of Sunitinib and CYP3A4 Inhibitors

Coadministration of ketoconazole (400 mg QD for 7 days), a potent CYP3A4 inhibitor, with SU011248 (single 10 mg) resulted in significant increases ($p<0.05$) in the mean C_{max} and $AUC_{0-\infty}$ values for SU011248 (Study RTKC-0511-009). Significant increases in Mean C_{max} and mean $AUC_{0-\infty}$ were seen in both Caucasians and Asians (see Tables). The apparent difference in clearance between Caucasians and Asians was related to differences in body weight as body-weight-normalized clearances were not different between the Caucasians and Asians.

Table 24: Mean ± SD (%CV) Pharmacokinetic Parameters for Sunitinib in Caucasian and Asian Male Subjects with and without Ketoconazole.

Treatment	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng.h/mL)	t½ (h)	CL/F (L/h)
Caucasian Subjects (n=12)*					
Sunitinib	4.3±1.1 (25%)	7.9±2.9 (37%)	216± 61 (28%)	41.2±7.7 (18%)	49.8±14.6 (29%)
Sunitinib+ Ketoconazole	7.0±1.5 (21%)	7.2±0.4 (5%)	392±86 (22%)	43.5±7.9 (18%)	26.8± 6.9 (25%)
p-value	<0.05		<0.05		
Asian Subjects (n=14, 3 Indian, 11 Chinese)					
Sunitinib	5.2±0.99 (19%)	8.9±3.1 (35%)	312±99 (32%)	43.2±9.4 (22%)	34.9±10.1 (28%)
Sunitinib+ Ketoconazole	8.1±1.5 (18%)	8.6±2.6 (30%)	507±120 (24%)	43.9±9.5 (22%)	20.8±5.0 (24%)
p-value	<0.05		<0.05		

One Caucasian subject discontinued from the study upon admission to Period II due to a positive drug screen

The mean C_{max} and $AUC_{0-\infty}$ values for SU012662 showed small decreases in both Caucasians and Asians when ketoconazole was co-administered with SU011248.

Table 25: Mean ± SD (%CV) Pharmacokinetic Parameters for SU012662 in Caucasian and Asian Male Subjects with and without Ketoconazole.

Treatment	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)
Caucasian Subjects (n=12)*				
Sunitinib	0.57±0.14 (24%)	9.2±12.3 (133%)	63.2±15.9 (25%)	82.7±16.2 (19%)
Sunitinib+ Ketoconazole	0.43±0.075 (17%)	23.3±19.8 (85%)	59.9±13.3 (22%)	83.3±19.6 (23%)
p-value	<0.05		>0.05	
Asian Subjects (n=14, 3 Indian, 11 Chinese)				
Sunitinib	0.61±0.12 (19%)	23.3±19.1 (82%)	88.2±16.3 18%)	82.5±16.9 20%)
Sunitinib+ Ketoconazole	0.41±0.11 (27%)	41.1±14.8 (36%)	73.0±15.1 (21%)	97.7±24.7 (25%)
p-value	<0.05		>0.05	

One Caucasian subject discontinued from the study upon admission to Period II due to a positive drug screen

The following table shows the effect of ketoconazole on the combined Cmax (parent+metabolite) and combined AUC (parent+metabolite) across all subjects. There was a 49% increase in combined Cmax and 51% increase in combined AUC related to ketoconazole.

Table 26: Mean±SD (%CV) Pharmacokinetic Parameters for the combined drug (sunitinib+SU012662) in All Subjects (n=26) with and without Ketoconazole.

Treatment	$AUC_{0-\infty}$ (parent) (ng.hr/mL)	$AUC_{0-\infty}$ (metabolite) (ng.hr/ml)	Combined $AUC_{0-\infty}$ (ng.h/mL)
Sunitinib	267.8 ± 95.4 (36%)	77.1 ± 20.5 (27%)	344.9 ± 112.2 (33%)
Sunitinib+ Ketoconazole	454.1 ± 118.6 (26%)	67.0 ± 15.5 (23%)	521.1 ± 128.1 (25%)

Based on the exposure-toxicity relationships described above, the increase in risk of various severe 3/4 toxicities following the recommended 50 mg dose is illustrated in the following figure. Risk for severe grade 3/4 fatigue would increase from 7% to 12%, while risk of severe neutropenia would increase from 12 to 17% and risk of severe anemia would increase from 23% to 30%.

To adjust for this increase, it is recommended that the sunitinib dose be reduced to 37.5 mg. [fold increase in AUC=521/345=1.5, therefore normal dose should be reduced to 66% of the recommended daily dose.]

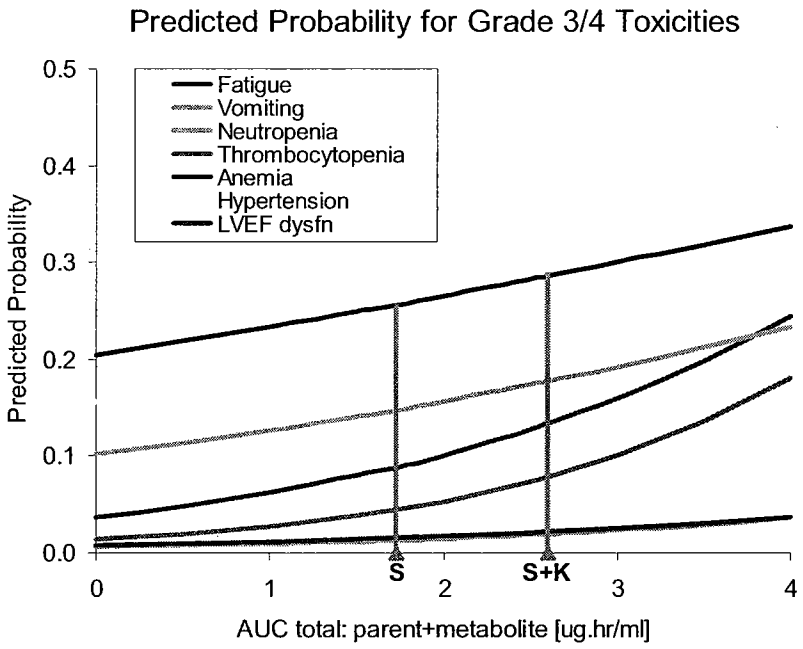


Figure 22: Predicted probabilities for various toxicities as a function of combined AUC of sunitinib and its active metabolite SU012662. Red triangles indicate the average AUC corresponding to a typical 50 mg dose in the absence (S) and in the presence of ketoconazole (S+K). The figure illustrates the increase in risk for the various toxicity measures as a result of the increased exposure following coadministration of ketoconazole.

Coadministration of Sunitinib and CYP3A4 Inducers

Concurrent administration of rifampin (600 mg QD for 17 days), a potent CYP3A4 inducer, with sunitinib (single 50 mg) resulted in a significant decreases ($p<0.05$) in the mean C_{max} and $AUC_{0-\infty}$ values for sunitinib (Study A6181001). Mean C_{max} and mean $AUC_{0-\infty}$ decreased signficiantly in Caucasians and in Japanese subjects in the presence of rifampin compared to sunitinib alone (see table below).

Table 27: Mean ± SD (%CV) Pharmacokinetic Parameters for SU011248 in Caucasian and Japanese male and female subjects with and without Rifampin.

Treatment	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng.h/mL)	t½ (h)	CL/F (L/h)
Caucasian Subjects (n=13)					
Sunitinib	27.1±5.3 (19%)	8.5±1.7 (20%)	1145±427 (37%)	48.5±10.2 (21%)	41.3±8.6 (21%)
Sunitinib+ Rifampin	12.7±2.9 (23%)	7.8±0.80 (10%)	281±55.9 (19%)	15.9±2.7 (17%)	184±37.5 (20%)
p-value	<0.05		<0.05		
Japanese Subjects (n=12)					
Sunitinib	33.4±7.6 (23%)	7.9±1.4 (18%)	1396±343 (24%)	49.5±12.5 (25%)	37.6±7.9 (21%)
Sunitinib+ Rifampin	14.2±3.7 (26%)	7.2±0.43 (6%)	290±70.8 (24%)	14.5±1.7 (12%)	180±37.9 (21%)
p-value	<0.05		<0.05		

The mean C_{max} and $AUC_{0-\infty}$ values for SU012662 increased in both Caucasians and Japanese subjects when rifampin was co-administered with sunitinib (see table below).

Table 28: Mean ± SD (%CV) Pharmacokinetic Parameters for SU012662 in Caucasian and Japanese male and female Subjects with and without Rifampin.

Treatment	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng.h/mL)	t½ (h)
Caucasian Subjects (n=13)				
Sunitinib	5.1±1.0 (20%)	7.5±2.4 (32%)	532±136 (25%)	81.4±16.3 (20%)
Sunitinib+ Rifampin	12.7±2.7 (21%)	5.4±1.9 (37%)	674±145 (21%)	65.4±20.7 (32%)
p-value	<0.05		<0.05	
Japanese Subjects (n=12)				
Sunitinib	7.3±1.8 (25%)	8.4±5.3 (63%)	692±159 (23%)	75.3±14.7 (19%)
Sunitinib+ Rifampin	16.8±4.2 (25%)	6.1±1.7 (29%)	877±188 (21%)	59.5±12.1 (20%)
p-value	<0.05		<0.05	

The following table shows the effect of rifampin on the total Cmax (parent+metabolite) and total AUC (parent+metabolite) across all subjects. There was a 23% decrease in total Cmax and 46% decrease in the combined AUC related to rifampin.

To adjust for this decrease, it is recommended that the sunitinib dose be increased to ~200% of the recommended dose. [fractional decrease in AUC=1049/1936=0.54, therefore normal dose should be increased to 50/0.54=90mg → 87.5 mg)]

Table 29: Mean±SD (%CV) Pharmacokinetic Parameters for the combined Drug (sunitinib+SU012662) in All Subjects (n=25) with and without Rifampin.

Treatment	$AUC_{0-\infty}$ (parent) (ng.hr/mL)	$AUC_{0-\infty}$ (metabolite) (ng.hr/ml)	combined $AUC_{0-\infty}$ (ng.h/mL)
Sunitinib	1327.5 ± 309.8 (23%)	609.3 ± 166.1 (27%)	1936.8 ± 418.0 (22%)
Sunitinib+ Rifampin	283.6 ± 62.9 (22%)	766.2 ± 192.2 (25%)	1049.9 ± 235.9 (22%)

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Sunitinib malate is classified as a Class IV compound (Low solubility-Low permeability) according to the Guidance for industry on Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS). Available at (http://www.fda.gov/cder/guidance/3618fnl.pdf).

The Applicant has determined the equilibrium solubility of sunitinib malate in standard aqueous buffer solutions at 37 °C. An aqueous solubility of — ng/mL for the 50-mg recommended dose (— mg of sunitinib malate in — mL media) is achieved across the range pH 1.2 to pH 6.8. Above pH 6.8, the solubility of sunitinib malate reduces rapidly and by pH 7.5 is — mg/mL. Therefore, sunitinib malate can be described as a low solubility drug.

The Applicant has evaluated the permeability of sunitinib and SU012662 across Caco-2 cells (Study SU011248-PDM-092). The permeability of sunitinib malate was compared to metoprolol (a high permeability standard) using a Caco-2 cell model. The apical to basolateral permeability values (P_{app}) is 3.8×10^{-6} cm/s for sunitinib malate using a concentration of 10 µM at pH 7.4. This value is less than that obtained for metoprolol (62×10^{-6} cm/s at 10 µM at pH 7.4). Based on these data, sunitinib malate is classified as a low permeability compound according to the BCS Guidance.

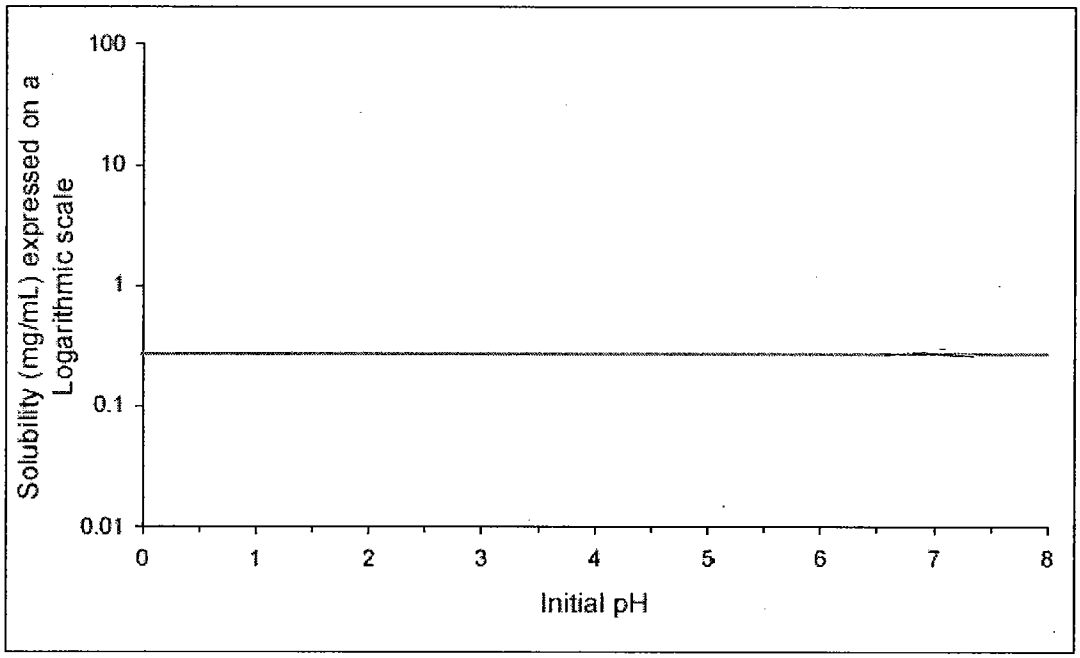


Figure 23: Equilibrium Solubility Profile for Sunitinib Malate at 37°C

Table 30: Mean ± SD apparent permeability coefficients (P_{app} x 10^{-6} cm/sec) for SU011248 and SU012662

Compound	Concentration (μM)	P_{app} A>B (x 10^{-6} cm/sec)
SU011248	1	2.2±0.51
	10	3.8±1.54
SU012662	1	1.1±0.07
	10	0.77±0.25
Metoprolol	10	62

2.5.2 What is the composition of the to-be-marketed formulation?

The formulation of the capsules used in the exploratory bioavailability studies differs from the clinical and proposed commercial formulations. The proposed commercial formulation is identical to the same strength clinical formulation. Between strengths, the formulations are different. The 12.5 mg capsule uses a blend formula containing [ ] w/w sunitinib malate, whereas the 25 mg and 50 mg capsule formula use a blend containing [ ] w/w sunitinib malate. The composition of the capsules, exploratory, clinical and proposed commercial, are given in the following table.

Table 31: Composition of SUTENT capsules.

	Exploratory Capsule Formulations				Clinical and Proposed Commercial Capsule Formulations		
Drug Substance	Sunitinib, free base	Sunitinib, free base	Sunitinib, free base	Sunitinib malate	Sunitinib malate	Sunitinib malate	Sunitinib malate
Strength (in mg, as sunitinib, free base)	50	75	200	50	12.5	25	50
Drug load (%)	[						]
Excipients (%) Mannitol Povidone Croscarmellose sodium Magnesium stearate	[						]
Capsule							
Size	#1	#1	#0	#3	#4	#3	#2
Cap color	Orange	Orange	Orange	Orange	Orange	Caramel	Caramel
Body color	Orange	Orange	Orange	Orange	Orange	Orange	Caramel

Data source: Module 3, Table 3.2.P.2-5.

[a] Sunitinib malate capsules, 25 mg, Size #3 of Orange cap and body color have also been used in clinical studies.

The qualitative and quantitative composition of the clinical and proposed commercial formulations are identical, differing only in the color of the 25-mg capsule shell, the ingoing drug substance particle size and the route of synthesis for the drug substance used, as described in the following table:

Table 32: Characteristic Differences in the Clinical and Proposed Commercial Sunitinib Formulations

Characteristic	Clinical Formulation	Proposed Commercial Formulation
25-mg capsule shell color		
Cap	Orange	Caramel Opaque
Body	Orange	Orange
Ingoing drug substance particle size[a]		
Drug substance route of synthesis		

The change in capsule shell color has no impact on the performance of the drug product. The drug substances produced via Methods [ ] utilize the same starting materials, produced by either method, meets the same specification. The impact of drug substance particle size on in vitro performance was evaluated in a bioequivalence study and was found to have no impact on the in vivo performance.

2.5.3. What is the in vivo relationship of the proposed to-be- marketed formulation to the pivotal clinical trial formulation?

The proposed 50 mg to-be-marketed formulation is bioequivalent to the clinical trial 50 mg formulation. The applicant conducted two bioavailability/bioequivalence studies to determine the bioequivalence of the proposed commercial formulations to the clinical formulation of sunitinib malate capsules. The proposed to-be-marketed formulation of the 50 mg sunitinib malate capsules and the to-be-marketed formulation of the 12.5 mg sunitinib malate capsules are bioequivalent to their respective strength clinical formulations. In addition, four 12.5 mg sunitinib malate capsules are bioequivalent to a single 50 mg sunitinib malate capsule. The 25 mg capsule is made from the same formula blend as the 50 mg capsule and is placed in the same capsule with the same excipients. The proposed 25 mg commercial formulation of sunitinib malate capsules is bioequivalent to the 50 mg clinical formulation based on comparable dissolution profiles.

Sunitinib free base or malate salt formulations administered as a capsule of 50 mg are bioequivalent. The pharmacokinetic profile of sunitinib is comparable when administered as a capsule or as a solution. Changes in drug particle size [redacted] during formulation development had no significant impact on the in vivo performance.

2.5.4 What moieties should be assessed in bioequivalence studies?

The bioequivalence studies should assess the parent compound, sunitinib.

2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A high-fat meal did not significantly affect the bioavailability of SU011248. The geometric least squares mean ratios and 90% CI (fed/fasted) for the primary PK parameters (sunitinib AUC0-last, AUC0-inf, and Cmax) fell within the 80% to 125% bioequivalence range. Sunitinib Tmax was not affected by the presence of food. In the case of the major metabolite SU012662, its rate of formation and/or absorption was decreased by food (23%, 30%, and 18% mean decrease in Cmax, AUC0-24, and AUC0-72, respectively, and the Tmax was increased from 12 hours (4.00-36.00) to 36 hours (8.00-36.3) when sunitinib malate was dosed with food. The extent of exposure of the metabolite was unaffected since geometric least squares mean ratios and 90% CI for AUC0-last and AUC0-∞ were within the 80% to 125% range. The decrease in SU012662 Cmax is unlikely to be of clinical significance since SU012662 exposure accounts for only about 30% that of total active drug (sunitinib + SU012662). Sutent® can be administered without regard to food.

2.5.7 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The dissolution method development study provided adequate information regarding the release rate of the drug product. The studies have demonstrated the dissolution method for the testing of sunitinib malate capsules using USP II paddle apparatus rotating at — rpm in 900 mL of hydrochloric acid (0.1 M) held at 37°C ± 0.5°C is suitable for assessing capsule performance. The proposed method is acceptable. Data generated during method development and stability testing indicates that the specification proposed by the sponsor (Q= [ ] at 30 minutes) may not be sufficiently robust. A specification of Q= [ ] at 30 minutes is more appropriate for this product. The final recommended dissolution procedure and specification are:

Apparatus:	USP Apparatus II (Paddle Method)
Rotation Speed:	— rpm
Medium:	0.1M HCl
Volume:	900 mL
Analytical:	UV Spectroscopy
Tolerance:	Q= [ ] at 30 minutes

An [ ] method for dissolution testing was validated in comparison to the [ ] method. The analytical method is acceptable for determining the dissolution results.

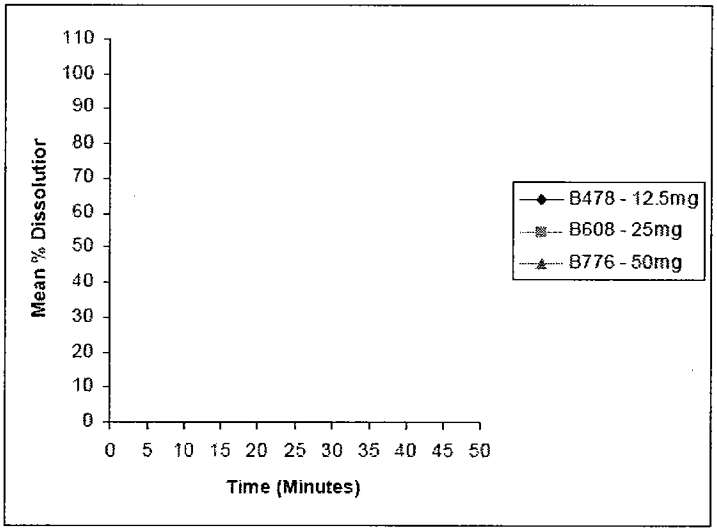


Figure 24: Dissolution profiles of sunitinib malate 12.5 mg, 25 mg and 50 mg capsules (pH 1.2, paddles at ~ rpm).

A waiver of the in vivo bioequivalence data necessary for the approval of the 25-mg strength sunitinib malate capsule was granted based on linear composition across the strengths to-be-marketed, the high solubility across the pH range of pH 1.2 to pH 6.8, and the in vitro dissolution comparison of the profiles generated for three 25-mg commercial batches and the 50-mg clinical trial formulation. Dissolution performance of the product was found to be comparable and across the media (pH 1.2 – pH 6.8).

2.5.8. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

There are no other significant, unresolved issues related to in vitro dissolution or in vivo bioavailability and bioequivalence that need to be addressed.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, 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.

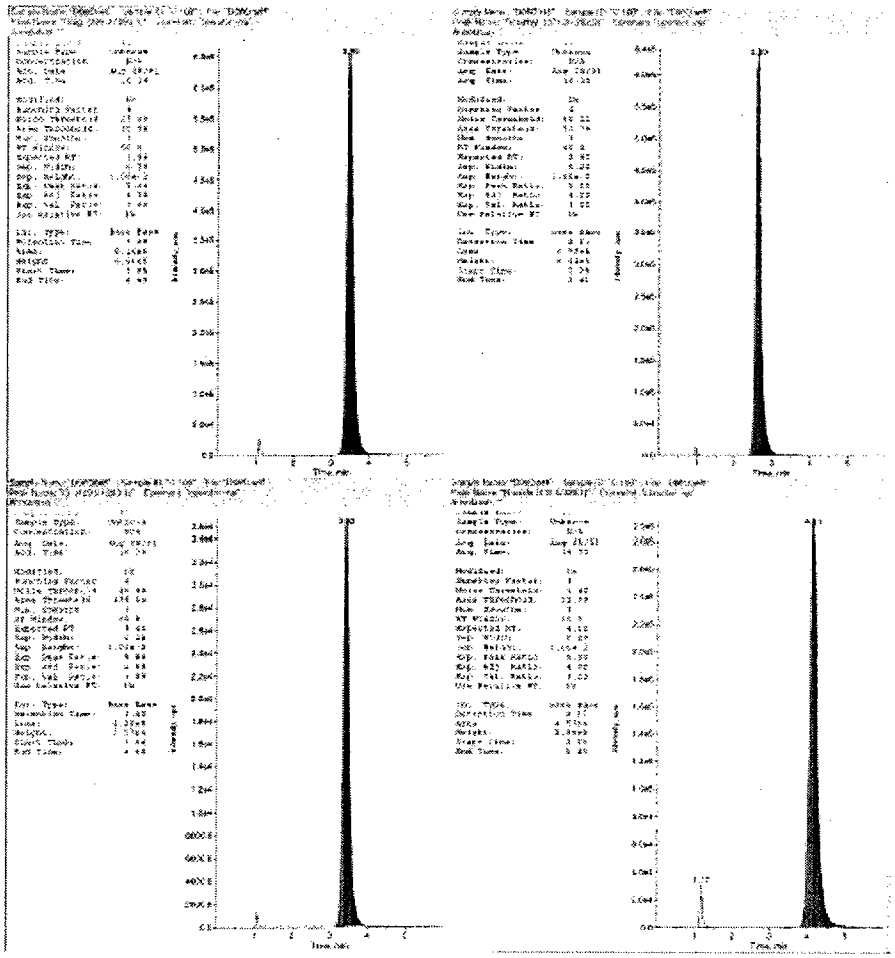
2.6.3 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes, the applicant developed and validated a LC/MS/MS method for the determination of sunitinib, SU012662, and SU012487 in [ ] human plasma. Sunitinib, SU012662, and SU012487 are extracted from plasma by protein precipitation extraction with methanol in a 96-well plate. Before the extraction, [2H10]-SU011248 is added as an internal standard. The [ ] The [ ] and [ ] using a [ ] The analytical method parameters are summarized in the following table.

Table 33: Analytical Method Performance for sunitinib, SU012662 and SU012487 in plasma using LC/MS/MS.

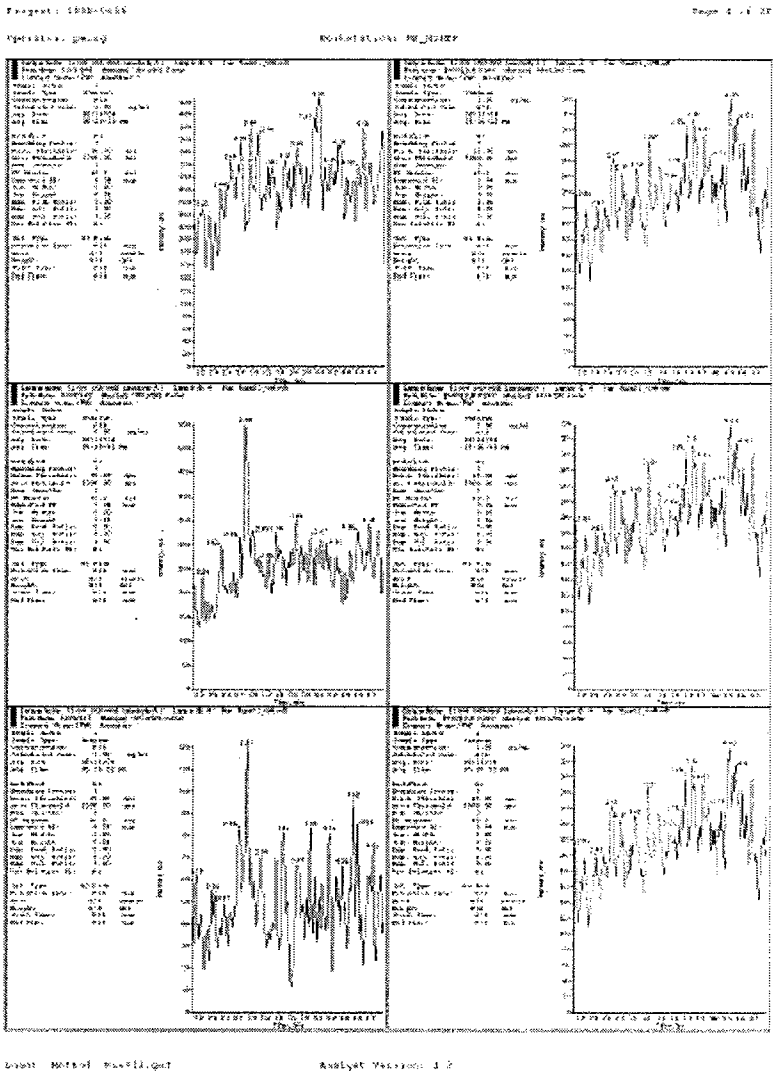
		SU011248	**SU012662**	**SU012487**
Analysis dates		Aug -2-01 to Aug-8-01		
Calibration curve		SU011248	SU012662	SU012487
	100 ng/mL	1.8%	4.5%	5.5%
	80 ng/mL	1.5%	3.5%	7.0%
	25 ng/mL	1.7%	3.3%	6.4%
	5 ng/mL	1.8%	4.2%	6.7%
	0.30 ng/mL	7.4%	4.9%	6.6%
	0.10 ng/mL	10.8%	5.2%	8.7%
Accuracy	100 ng/mL	101.4%	100.8%	102.3%
	80 ng/mL	99.0%	99.1%	97.4%
	25 ng/mL	99.5%	99.2%	98.0%
	5 ng/mL	101.2%	101.1%	101.0%
	0.30 ng/mL	98.4%	99.7%	102.0%
	0.10 ng/mL	108.5%	108.1%	99.1%
Correlation coefficient	N=4	0.99810	0.99888	0.99704
Intra-assay	80 ng/mL	5.5%	6.7%	9.6%
Precision	40 ng/mL	0.5%	3.8%	1.2%
N=24	0.300	4.8%	5.2%	4.1%
QC samples	80 ng/mL	3.0%	2.6%	4.2%
	40 ng/mL	0.5%	3.4%	10.0%
	0.300	2.7%	5.5%	13.6%
	80 ng/mL	3.3%	3.9%	3.4%
	40 ng/mL	2.4%	3.5%	4.1%
	0.300	4.5%	5.2%	2.4%
Intra-assay	80 ng/mL	102.4%	92.7%	87.1%
Accuracy	40 ng/mL	98.0%	97.0%	92.9%
N=24	0.300	97.0%	96.9%	89.6%
QC samples	80 ng/mL	108.4%	106.3%	109.5%
	40 ng/mL	98.7%	106.3%	104.7%
	0.300	101.7%	107.3%	101.7%
	80 ng/mL	104.5%	108.6%	108.0%
	40 ng/mL	100.1%	100.9%	106.7%
	0.300	96.5%	97.8%	103.7%
Inter-assay	80 ng/mL	3.8%	8.0%	10.2%
Precision	40 ng/mL	2.4%	5.1%	7.6%
N=24	0.300	4.3%	6.7%	11.6%
Inter-assay	80 ng/mL	102.1%	102.4%	101.4%
Accuracy	40 ng/mL	99.9%	102.9%	101.6%
N=24	0.300	99.3%	102.0%	99.0%
Limits of Quantitation	Lower	0.100 ng/mL	0.100 ng/mL	0.100 ng/mL
	Upper	100 ng/mL	100 ng/mL	100 ng/mL
Specificity	6 lots of matrix	No greater than 5%	No greater than 5%	No greater than 5%
Extract Stability	QC samples RT/dark/73 hrs	Met precision and accuracy criteria	Met precision and accuracy criteria	Met precision and accuracy criteria
	Freeze/Thaw -20°C for ● cycles	Met precision and accuracy criteria	Met precision and accuracy criteria	Met precision and accuracy criteria
Stock Standard Stability	4°C for 19 days	Met % difference criteria	Met % difference criteria	Met % difference criteria

Batch Run 45



[1] In the chromatograms presented in Figures 1 - 3, from left to right, the upper row represents SU011248 and SU012662 and the lower row represents the internal standard and SU012487.

Figure 25: Typical chromatograms for High Calibration Standard.



[1] In the chromatograms presented in Figures 5, the top left panel represents SU011248, the middle left panel represents SU012662, the bottom left panel represents SU012487, and the right panels represents the internal standard.

Figure 26: Chromatograms of selectivity. Left panels show blank matrix injections for sunitinib (upper panel), SU012662 (middle panel) and SU012487 (bottom panel). Left panels correspond to samples and right panels represents the internal standard.

3. DETAILED LABELING RECOMMENDATIONS

Proposed changes highlighted with blue underline and strike-through.

1. Under CLINICAL PHARMACOLOGY/Pharmacokinetics

Applicant's labeling:

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

[ ]

FDA proposed labeling

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

Absorption, Distribution, Metabolism, and Elimination
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. Sunitinib may be taken with or without food.

Binding of sunitinib and its primary 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 gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (MRCC) (see CLINICAL STUDIES).

2. **Under CLINICAL PHARMACOLOGY/Special Populations**

Applicant's labeling

[

]

FDA proposed labeling

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 active metabolite.

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

3. **Under CLINICAL PHARMACOLOGY/Hepatic Insufficiency**

Applicant's labeling

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

]

FDA proposed labeling

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

4. **Under CLINICAL PHARMACOLOGY/Renal Insufficiency**

Applicant's labeling

[ ] No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered

[

]

FDA proposed labeling

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

5. **Under CLINICAL PHARMACOLOGY**

Applicant's labeling

Drug-Drug Interactions
In vitro studies indicate that sunitinib does not induce or inhibit major CYP enzymes.

In Vitro Studies of CYP Inhibition and Induction: 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.

CYP3A4 Inhibitors: Concurrent administration of sunitinib malate with the CYP3A4 inhibitor, ketoconazole, resulted in [ ], increases in [ ]

[

]

[

]

FDA proposed labeling

Drug-Drug Interactions
In vitro studies indicate that sunitinib does not induce or inhibit major CYP enzymes.

In Vitro Studies of CYP Inhibition and Induction: 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.

CYP3A4 Inhibitors: Concurrent administration of sunitinib malate 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 sunitinib malate in healthy volunteers. A dose reduction for SUTENT® should be considered when it must be co-administered with strong CYP3A4 inhibitors (see DOSAGE AND ADMINISTRATION).

CYP3A4 Inducers: Concurrent administration of SUTENT® with the 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. A dose increase for SUTENT® should be considered when it must be co-administered with CYP3A4 inducers (see DOSAGE AND ADMINISTRATION).

6. **UNDER PRECAUTIONS/Information for Patients**

Applicant's labeling

FDA Proposed labeling

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

Skin discoloration possibly due to the drug color (yellow) occurred in approximately 1/3 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.

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

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).

6. **UNDER PREACUTIONS/Drug interactions**

Applicant's labeling

[redacted]

FDA Proposed labeling

Co-administration of SUTENT® with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconizole) increases sunitinib concentrations. Grapefruit may also increase plasma concentrations of SUTENT® (see CLINICAL PHARMACOLOGY). Co-administration of SUTENT® with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) decreases sunitinib concentrations (see CLINICAL

PHARMACOLOGY). St. John's Wort may decrease SUTENT®™ plasma concentrations unpredictably. Patients receiving SUTENT®™ should not take St. John's Wort concomitantly. SUTENT® dose modification is recommended in patients using concomitant CYP3A4 inhibitors or inducers (see DOSAGE AND ADMINISTRATION).

7. **UNDER DOSAGE AND ADMINISTRATION**

Applicant's labeling

[ ] SUTENT may be taken with or without food.

Dose Modification

[

]

FDA Proposed labeling

The recommended dose of SUTENT® for GIST and advanced RCC is one 50-mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. SUTENT® may be taken with or without food.

Dose 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** SUTENT® 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 should be considered if SUTENT® must be co-administered with a strong CYP3A4 inhibitor (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions).

CYP3A4 inducers such as rifampin may **decrease** SUTENT® plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Dose increases in 12.5 mg increments to a maximum of 87.5 mg daily for SUTENT® 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 CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions). St. John's Wort may decrease SUTENT® plasma concentrations unpredictably. Patients receiving SUTENT® should not take St. John's Wort concomitantly.

21 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

4. SUMMARY OF BIOPHARMACEUTICS REVIEW

A. EXPLORATORY STUDIES

B. BIOAVAILABILITY STUDIES

C. ANALYTICAL METHOD VALIDATION REPORT: SUNITINIB IN PLASMA

D. DISSOLUTION METHOD DEVELOPMENT

E. WAIVER REQUEST

Individual Study Reviews

A. EXPLORATORY STUDIES

A1. Study 248-ONC-0511-001
Title: A Phase 1 mono-center, randomized, double-blind, ascending single dose study in healthy male subjects to assess the safety, tolerability and pharmacokinetics of SU011248

Principal Investigator: [

]

Dates: 12 December 2000 to 24 January 2001

Objectives

Primary: To assess the safety and tolerability of two ascending single oral doses of SU011248.
Secondary: To evaluate the pharmacokinetics of two ascending single oral doses of SU011248

Study Design:
This trial was planned as a mono-center, randomized, double-blind, placebo-controlled, ascending single dose study. The study used two groups of nine healthy male subjects. Six subjects per group received SU011248 and three subjects received placebo (apple juice).

Treatments: 50 mg SU011248 powder lot H82R02
50 mg SU011248 capsule lot H82G04 ([ ] capsule batch)

Pharmacokinetic Results:

Table A1.1 Study 248-ONC-0511-001: Sunitinib and SU012662 Pharmacokinetic Parameters Following a Single 50-mg Dose of Sunitinib

Pharamacokinetic Parameter	Mean (%CV)	
	Plasma Sunitinib (n=6)	Plasma SU012662 (n=6)
Cmax (ng/mL)	37.7 (24.6)	6.5 (26.1)
AUC0-last (ng*hr/mL)	943 (25.4)	183 (25.9)
AUC 0-inf (ng*hr/mL)	1350 (31.9)	444 (58.4)
CL/F (L/hr)	40.4 (32.0)	N/A
T ½ (hr)	26.9 (27.2)	57.5 (63.2)
Tmax (hr)[a]	6.00 (5.00, 16.00)	5.00 (4.5, 24.0)
[a] Median (min, max)		

Pharmacokinetic Evaluation:
Absorption of an oral 50-mg dose of SU011248 in six healthy subjects was relatively slow (Tmax reached within 5-7 hours). A second peak of similar height was observed in at least two subjects. Cmax and $AUC_{0\text{-inf}}$ values averaged 37 ng/mL and 943 ng•h/mL, respectively. The average, apparent elimination half-life

of 27 hours was also longer than expected from pre-clinical animal studies, so that the 48-hour observation period only covered 70% of the $AUC_{0\text{-}inf}$. Due to the unexpectedly high availability of SU011248 in man, the study was prematurely terminated at the 50-mg dose level. The metabolite SU012662 occurred at the same time in plasma as the parent compound and appeared to reach Cmax somewhat earlier than the parent compound, which may indicate a rapid pre-systemic elimination (first-pass). Plasma Cmax and AUC0-inf of the metabolite were approximately one sixth of the parent compound SUO11248.

Safety Evaluation: Physical examinations, blood pressure, pulse rate, 12-lead ECG, 24- hour Hotter ECG, Lead II ECG, routine blood and urine safety analysis, special safety laboratory and adverse events recording were used to assess safety. No clinically significant change from baseline occurred in any individual vital signs parameter.

A.2. Study 248-ONC-0511-004

Title: A Phase 1, Comparative Study of Bioavailability of Oral SU011248 as Either Free-Base or Malate Salt, and Effect of Food

Investigator: [redacted]

Dates: 10 June 2001 to 10 August 2001

Objective:
This study was conducted to provide a preliminary assessment of the effect of food on the oral BA of sunitinib using the malate salt capsule, and to assess the safety and tolerability of sunitinib.

Study Design:
A single-center, randomized, open-label, 3-way crossover study conducted to compare the oral BA of sunitinib following a single 50-mg dose delivered as a capsule containing free base or as a capsule containing the malate salt and to determine the effect of food on the malate salt capsule.

Treatment:
Fifteen healthy, white men (5 per treatment sequence), ages 22 to 38 years were enrolled in this study. Thirteen subjects completed all study procedures. Two subjects discontinued treatment due to AEs (intervertebral disk prolapse; pharyngitis not otherwise specified [NOS] with pyrexia) after the first treatment period.

Treatment A: Sunitinib free base, fasted: 50 mg batch H82G04 ([redacted] capsules batch)
Treatment B: Sunitinib malate, fasted: 50 mg batch I83G02 ([redacted] capsule batch)
Treatment C: Sunitinib malate salt, fed: 50 mg batch I83G02 ([redacted] capsule batch)

Sample Collection:
Serial blood samples were collected predose through 72 hours after dosing. Urine samples for PK analysis were collected at predose and over the following intervals: 0-24 hours, 24-48 hours, and 48-72 hours.

Pharmacokinetics: The primary PK endpoints for these comparisons were sunitinib AUC0-last and Cmax, and the secondary PK endpoint was sunitinib AUC 0-inf. At 10-day intervals, subjects received 3 doses of sunitinib 50 mg as a free-base capsule under fasted conditions, as a malate salt capsule under fasted conditions, and as a malate salt capsule under fed conditions (30% fat, 780 calories).

Pharmacokinetic Results:

Table A.2. 2: Summary of Sunitinib Pharmacokinetic Results by Treatment (Study 248-ONC-0511-004)

Table A.2.1: Summary of Sunitinib PK Results by Treatment (Study 248-ONC-0511-004)

Pharmacokinetic Parameter	Treatment			90% CI of Treatment Ratios	
	A Free Base, Fasted (n=14)b	B Malate Salt Fasted (n=13)	C Malate Salt Fed (n=14)b	B/A[a]	C/B[a]
Cmax (ng/mL)					
Geometric Mean	23.3	24.7	27.1	0.98-1.15	0.95-1.16
95% CI	20.0, 27.2	21.1, 28.9	22.7, 32.4		
AUC0-last (ng*hr/mL)					
Geometric Mean	937	1038	1177	1.02-1.16	1.00-1.18
95% CI	758, 1159	820, 1313	937, 1479		
AUC0-inf (ng*hr/mL)					
Geometric Mean	974	1059	1230	1.00-1.14	1.00-1.18
95% CI	796, 1192	836, 1341	964, 1570		
Tmax (hr)					
Median	7.25	6.00	6.75	N/A	N/A
Min, Max	[illegible]			[illegible]	

[a] The 90% CIs for the treatment ratios above have been mathematically converted from a comparison of Treatments A/B and B/C to a comparison of B/A and C/B, respectively.
[b] 13 subjects were PK evaluable per protocol definition. However, 14 subjects had samples available for analysis while on Treatments A and C.

The primary comparison, sunitinib malate, fasted (Treatment B) versus free base, fasted (Treatment A), was within the defined bioequivalence interval of 0.80 to 1.25 for Cmax, AUC0-last, and AUC0-inf. The secondary comparison of malate salt, fed (Treatment C) with malate salt, fasted (Treatment B) was also bioequivalent. The comparison of sunitinib free-base, fasted to sunitinib malate, fed is not presented since the free base will not be commercially available and, therefore, this comparison is not considered to be relevant.

C. BIOAVAILABILITY STUDIES

B.1. Study A6181032

Title: Phase 1 Open-Label Study to Compare the Pharmacokinetics of the Proposed Commercial 50 mg Capsule under Fasting and Fed Conditions in Healthy Subjects

Investigators: Thomas C. Stock, DO
Pfizer Research Clinic
Pfizer Global Research & Development-Ann Arbor Laboratories
2800 Plymouth Road
Ann Arbor, MI 48105

Dates: 28 October 2004 to 21 December 2004

Objective(s): The primary objective was to assess the effect of a high-fat meal and fasting on the bioavailability of the proposed commercial 50 mg SU011248 capsule formulation. The secondary objectives included documentation of collected safety endpoints of physical examination, vital signs, ECGs, safety laboratory tests, concomitant medications, and adverse event monitoring.

Study Design: This trial was an open-label, randomized, single-dose, 2-treatment (fed vs. fasting), 2-way crossover study in healthy subjects. Each subject received a single 50-mg, oral dose of the proposed commercial SU011248 formulation under fasted conditions or after consumption of a high-fat meal.

Treatment: Sixteen subjects (10 males, 6 females; 13 white, 2 black, and 1 race unlisted; ages 22 to 57 years) enrolled in the study and comprised the safety analysis population. Eight subjects (50%) were treated in Treatment Sequence 1-2 and eight were treated in Treatment Sequence 2-1. All sixteen subjects (100%) received Treatment 1 (a single dose of 50 mg under fasting conditions), and 14 subjects (88%) received Treatment 2 (a single dose of 50 mg under fed conditions). Two subjects (13%) discontinued the study because of adverse events after receiving Treatment 1 but before receiving Treatment 2.

Study Drugs and Lot Numbers			
Study Drug	**Dosage form**	**Lot number**	**Particle size**
Proposed Commercial	**50 mg sunitinib malate capsule**	**N0400287**	

The capsules were packaged in opaque plastic bottles to protect the compound from light)

Treatment 1, fasted state: subjects received a 50 mg capsule of SU011248 at approximately 0800 hours, following a 10-hour fast.

Treatment 2, fed state: subjects received a 50 mg of SU011248 capsule at approximately 0800 hours within 30 minutes following the high-fat/high-calorie breakfast meal (approximately 800 to 1000 calories), which consisted of the following:

2 eggs fried in butter,
2 strips of bacon,
2 slices of toast with (2 pats) butter,
4 ounces of hash brown potatoes,
8 fl. oz. (240 mL) of whole milk
(i.e., approximately 150 protein calories, 500-600 fat calories).

Investigator site personnel administered SU011248 during each session with 240 mL ambient temperature water. Subjects swallowed the trial medication whole.

Sample Collection: collections for PK were performed at the following time points:
Hour 0 (pre-dose), Hours 1, 2, 4, 8, 12, 16 (Day 1), Hours 24, 36 (Day 2), Hour 48 Day 3), Hour 72 (Day 4), Hour 96 (Day 5), Hour 120 (Day 6), Hour 144 (Day 7), Hour 168 (Day 8), Hour 192 (Day 9), Hour 240 (Day 11), Hour 288 (Day 13), Hour 360 (Day 16), Hour 408 (Day 18), Hour 432 (Day 19), Hour 456 (Day 20), and Hour 480 (Day 21) post-dose

Safety Evaluation:
Evaluation of the safety of the dosage was based on results of the following tests: serum chemistry, hematology, and urinalysis. Subjects were also screened for drugs. Adverse events were listed and evaluated. 14 subjects (88%) experienced adverse events; no subject experienced a serious adverse event; and 10 subjects (63%) experienced treatment-related adverse events including headache (5 subjects); pruritis (5 subjects); dyspepsia (2 subjects); vaginosis fungal (2 subjects) and rash (2 subjects). All adverse events were CTCAE grade 1 or 2 and all events resolved except for one unrelated event (grade 1 muscle twitching). Two subjects discontinued the study because of adverse events; both subjects completed all visits of Treatment Study Period 1 (fasting) but discontinued before Treatment 2.

Analytical Method Performance:
Human K3EDTA plasma samples were assayed for the determination of SU011248 and SU012662 concentrations using a validated, sensitive and specific isocratic liquid chromatographic tandem mass spectrometric (LC/MS/MS) method in the positive ionization mode. The analytical method performance parameters are shown in table B.1.2.

Table B.1.2: Assay Performance Parameters for Study A6181032

Specificity	Chromatogram	Specific for sunitinib	Specific for SU012662
Linearity	Correlation Coefficient	0.997186	0.992885
Reproducibility (standard)	Inter- run %CV	2.4% - 4.2%	3.1% - 7.3%
Accuracy (Standards)	Inter-run %Bias	-1.8 to -3.6	-3.8% to 4.8%
Reproducibility (QC samples)	Inter-run % CV	2.4% - 6.59%	3.7% - 11.1%
Accuracy (QC samples)	Inter-run %Bias	-1.3% to -1.3%	-1.7% to -2.3%

Pharmacokinetics: Plasma PK parameter values were calculated by noncompartmental analysis of concentration-time data using WinNonlin Version 3.2. Actual sample collection times were used for PK analysis. All concentrations assayed as below the limit of quantification (BLQ) were set to zero.

Statistical Evaluation:
Statistical models were used to compare the bioavailability of the SU011248 commercial formulation under fed versus fasted conditions, for all PK evaluable subjects. A linear mixed-effects statistical model was fit to each log-transformed PK parameter. The model included factors accounting for the following sources of variation: sequence, subject nested in sequence, period, and treatment. The difference in the means of each log-transformed PK parameter (fed – fasted) and 90% confidence intervals (CI) on this difference were calculated, and then back-transformed to obtain the ratio of the geometric least squares means and corresponding 90% CI for that parameter. Subjects who had PK parameters for at least 1 treatment were included in the statistical comparisons of PK parameters. A similar model was used to analyze all secondary PK parameters (SU011248: AUC0-24, AUC0-72, t1/2, and CL/F; SU012662: Cmax, AUC0-last, AUC0-inf, AUC0-24, AUC0-72 and t1/2). Median values and ranges were presented for Tmax. The analysis of Tmax followed the nonparametric Hauschke, Steinjans, and Diletti procedure. First, within each sequence and for each subject, the difference in Tmax between the 2 periods was calculated. Next, all possible pairwise combinations of observed differences between the first sequence and second sequence were created (eg. Patient X, from Sequence 1-2, their difference in Tmax is paired with every patients recorded deference in Sequence 2-1). Finally, the difference in the differences between sequences is calculated and the median, minimum, and maximum values were reported.

RESULTS

Table B.1.3 below summarizes SU011248 and SU012662 PK parameters for each treatment, and the results of statistical comparisons between treatments.

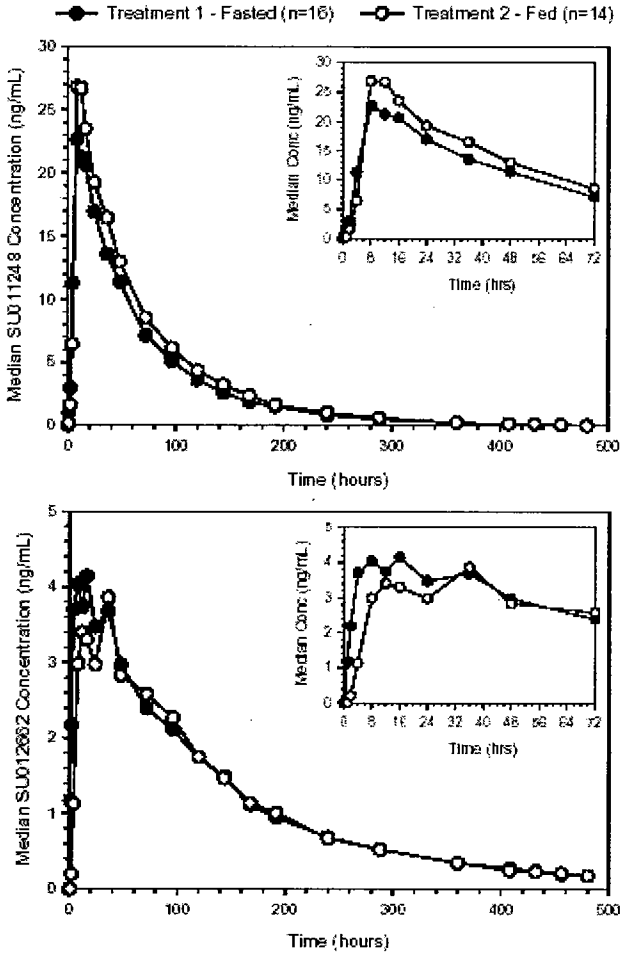
Table B.1.3 Summary of SU011248 and SU012662 Pharmacokinetic Parameters Following Dosing with the 50-mg SU011248 Proposed Commercial Formulations Under Fed and Fasted Conditions and Results of Statistical Comparisons Between Treatments

Parameter	Geometric Mean (95% CI)		Statistical Comparison (Fed/Fasted) [a]	
	Treatment 1 (Fasted) (n=16)	Treatment 2 (Fed) (n=14)	Geom. LS Mean Ratio (%)	90% CI (%)
PRIMARY PK PARAMETERS				
SU011248				
C_{max} (ng/mL)	25.1 (21.1, 29.7)	27.6 (23.8, 32.0)	104	97, 111
$AUC_{0\text{-last}}$ (ng*hr/mL)	1476 (1264, 1724)	1751 (1494, 2053)	112	108, 116
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	1489 (1276, 1736)	1765 (1506, 2069)	112	108, 116
SECONDARY PK PARAMETERS				
SU011248				
$AUC_{0\text{-}24}$ (ng*hr/mL)	422 (362, 491)	456 (399, 521)	102	98, 107
$AUC_{0\text{-}72}$ (ng*hr/mL)	968 (838, 1118)	1113 (975, 1271)	109	105, 112
CL/F (L/hr)	33.6 (28.8, 39.2)	28.3 (24.2, 33.2)	90	86, 93
$t_{1/2}$ (hr)	59.1 (53.4, 65.3)	61.4 (56.2, 67.1)	103	96, 110
T_{max} (hr)	8.03 (8.00, 16.0) [b]	8.03 (8.00, 12.0) [b]	0.02 [c]	-1.99, 2.02 [c]
SU012662				
C_{max} (ng/mL)	4.46 (3.50, 5.70)	3.53 (2.92, 4.27)	77	69, 86
$AUC_{0\text{-last}}$ (ng*hr/mL)	573 (487, 675)	544 (453, 654)	92	89, 96
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	606 (518, 708)	575 (480, 688)	92	89, 96
$AUC_{0\text{-}24}$ (ng*hr/mL)	82.5 (66.4, 103)	58.9 (48.8, 71.0)	70	64, 77
$AUC_{0\text{-}72}$ (ng*hr/mL)	231 (188, 283)	194 (160, 234)	82	76, 87
$t_{1/2}$ (hr)	104 (91.7, 117)	106 (94.0, 120)	103	100, 107
T_{max} (hr)	12.0 (4.00, 36.0) [b]	36.0 (8.00, 36.3) [b]	2.00 [c]	-13.9, 18.2 [c]

Geom. LS mean – geometric least squares mean; CI – confidence interval.
Treatment 1 = 50-mg proposed commercial formulation of SU011248 under fasting conditions; Treatment 2 = 50-mg proposed commercial formulation of SU011248 under fed conditions.
a Geometric least squares ratio and 90% confidence intervals from mixed effects model comparing fed (test) to fasted (reference) treatments.
b Median (min, max).
c Median difference and range (in hours) from statistical comparison of T_{max} using Hauschke, Steinijans, and Diletti's method.

Plasma concentration-time profiles for SU011248 and SU012662 under fed and fasted conditions are illustrated by the following Figures 1. Figure shows plots of individual AUC0-inf and Cmax values and the geometric means and 95% confidence intervals for SU011248 and SU012662 following oral administration of a 50-mg SU011248 proposed commercial formulation under fed and fasted conditions.

Figure 1. Linear Plots of Median Plasma SU011248 and SU012662 Concentration-time Profiles in Healthy Subjects Following Treatment with the 50-mg SU011248 Proposed Commercial Formulation Under Fasted and Fed Conditions



Note: Treatment 1 = 50-mg proposed commercial formulation of SU011248 under fasting conditions (reference); Treatment 2 = 50-mg proposed commercial formulation of SU011248 under fed conditions (test).The inset plots show an expanded view of the 0-72 hour time period.

Conclusions

The results of this study demonstrated that a high-fat meal did not significantly affect the bioavailability of SU011248. The geometric least squares mean ratios and 90% CI (fed/fasted) for the primary PK parameters (SU011248 AUC0-last (108%-116%), AUC0-inf (108%-116%), and Cmax (97%-111%)) fell within the 80% to 125% bioequivalence range. SU011248 Tmax was not affected by the presence of food. In the case of the metabolite SU012662, its rate of formation and/or absorption was decreased by food (23%, 30%, and 18% mean decrease in Cmax, AUC0-24, and AUC0-72, respectively, and a 24-hour prolongation of Tmax), but its extent of exposure was unaffected since geometric least squares mean ratios and 90% CI for AUC0-last and AUC0-∞ were within the 80% to 125% range. The decrease in SU012662 Cmax is unlikely to be of clinical significance since SU012662 exposure accounts for only about 30% that of total active drug (SU011248 + SU012662). The mean half-lives of SU11248 and

SU012662 in this study were approximately 60 hours and 105 hours, respectively. Multiple peks were observed in SU012662 plasma concentrations in many subjects, resulting in variable Tmax estimates for this analyte. Results of safety laboratory assessments, vital signs assessments, and ECG assessments did not indicate any unexpected risks of SU011248 under either fed or fasting conditions.

B.2. Study A6181033

Title: Phase 1 Open-Label Study to Compare the Pharmacokinetics of SU011248 Administered as One Clinical Trial 50-mg Capsule, One Proposed Commercial 50-mg Capsule and Four Proposed Commercial 12.5-mg Capsules in Healthy Subjects

Investigators: [redacted]

Dates: 16 September 2004 to 10 January 2005

Objective(s):

1. To establish the bioequivalence of the proposed commercial 50-mg SU011248 capsule to the clinical trial 50-mg SU011248 capsule; and
2. To establish bioequivalence of 4 proposed commercial 12.5-mg capsules to 1 clinical trial 50-mg capsule.

Design: This trial was an open-label, randomized, single-dose, 3-way crossover study in healthy subjects. Twenty-five subjects enrolled in the study and comprised the safety analysis population. There were 4 subjects in Treatment 1-2-3, Treatment 1-3-2, Treatment 2-1-3, Treatment 2-3-1 and Treatment 3-1-2, and 5 subjects in Treatment 3-2-1. Twenty-four subjects (96%) had at least 1 calculable PK parameter and were included in the evaluable PK population. Each subject received a single 50-mg, oral dose of each formulation (the proposed commercial formulation or the clinical trial formulation) and a single dose consisting of four 12.5 mg capsules of the proposed commercial formulation. Each treatment period included 21 days of monitoring after dosing. In addition, each treatment period was administered under fasting condition and followed by a 7- to 14-day washout before the next treatment period. Twenty-two subjects (88%) completed the study per protocol, 2 subjects (8%) discontinued prematurely because of adverse events, and 1 (4%) discontinued because of consent withdrawal.

Study Treatment: The following batches of sunitinib malate salt capsules were used:

Study Drugs and Lot Numbers				
Treatment	Study Drug	Dosage form	Lot number	Particle size
1	Clinical trial, 50 mg	50 mg sunitinib malate capsule	N0400278	
2	Proposed Commercial	50 mg sunitinib malate capsule	N0400287	
3	Proposed Commercial	12.5 mg sunitinib malate capsule	N0400280	

Sample Collection:

Serial blood samples were collected predose, and at Hours 1, 2, 4, 8, 12, 16, 24, 36, and then daily (except Days 10, 12, 14, 15, and 17) through Day 21 of each period. All efforts were made to obtain the PK samples at the exact nominal time relative to dosing.

Safety Evaluation:
Evaluation of the safety of the dosage was based on results of the following tests: serum chemistry, hematology, and urinalysis. Subjects were also screened for drugs. Adverse events were listed and evaluated. Five subjects experienced 3 clinically significant (grade 3 or 4) adverse events (pharyngitis, gasteroenteristis, and headaches). There were no deaths or post treatment serious adverse events, and all adverse events resolved without treatment. Two subjects discontinued because of adverse events and 1 subject discontinued because of consent withdrawal. Results of safety laboratory assessments, vital signs assessments, and ECG assessments did not indicate any unexpected risks of SU011248 when administered either as the clinical or commercial formulations.

Analytical Method Performance:
Human K3EDTA plasma samples were assayed for the determination of SU011248 and SU012662 concentrations using a validated, sensitive and specific isocratic liquid chromatographic tandem mass spectrometric (LC/MS/MS) method in the positive ionization mode. The analytical method performance parameters are shown in table B.2.2.

Table B.2.2: Assay Performance Parameters for Study A6181033

Specificity	Chromatogram	Specific for sunitinib	Specific for SU012662
Linearity	Correlation Coefficient	0.994898	0.991718
Reproducibility (standard)	inter- run %CV	2.2 to 4.5%	3.8% - 5.7%
Accuracy (Standards)	Inter-run %Bias	-1.8 to -3.6	-3.1% to 4.4%
Reproducibility (quality control samples)	Inter-run % CV	2.5% - 8.5%	4.4% - 9.7%
Accuracy (QC samples)	Inter-run %Bias	-1.3% to -2.4%	-0.3% to -2.8%

Pharmacokinetics: The following parameters were calculated for SU011248 and its metabolite, SU012662: Cmax, Tmax, AUC0-last (area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration), AUC0-∞, t1/2 (half-life), AUC0-24, AUC0-72, and CL/F (oral clearance, calculated for SU011248 only). Plasma PK parameter values were calculated by noncompartmental analysis of concentration-time data using WinNonlin Version 3.2. Actual sample collection times were used for PK analysis. All concentrations assayed as below the limit of quantification (BLQ) were set to zero.

Statistical Evaluation:
Statistical models were fit to determine the bioequivalence between the 50-mg proposed commercial formulation (test) versus the 50-mg clinical trial formulation (reference), and between the 4 x 12.5-mg proposed commercial formulation (test) versus the 50-mg clinical trial formulation (reference), for all PK evaluable subjects. The primary PK parameters used to evaluate bioequivalence were SU011248 Cmax, AUC0-last, and AUC0-∞. A linear mixed-effect statistical model, which included factors accounting for the sources of variation, sequence, subject nested in sequence, period, and treatment, was fit to each log-transformed PK parameter. For each comparison of interest (test vs. reference), the difference in the

means of each log-transformed pharmacokinetic parameter (test – reference) and 90% CIs on this difference were calculated, and then back-transformed to obtain the ratio of the geometric least squares means and corresponding 90% CI for that parameter. Median values and ranges were presented for Tmax. The analysis of Tmax followed the nonparametric Hauschke, Steinjans, and Diletti procedure. First, within each sequence and for each subject, the difference in Tmax between the two periods was calculated.

Pharmacokinetic Results:

Table B.2.2 summarizes SU011248 and SU012662 PK parameters for each treatment, and the results of statistical comparisons between treatments.

Table B.2.2: Summary of Sunitinib and SU012662 PK Parameters for the 50-mg Sunitinib Clinical Trial Formulation and the 4 X 12.5 mg and 50 mg Sunitinib Proposed Commercial Formulations and Results of Statistical Comparisons Between Formulations (Study A6181033)

Pharmacokinetic Parameter	Geometric Mean (95% CI)						Geometric LS Mean Ratio (%)[a] (90% CI)			
	Treatment 1 (n = 23)		Treatment 2 (n = 22)		Treatment 3 (n = 23)		Treatment 2/1		Treatment 3/1	
SU011248										
C_{max} (ng/mL)	29.9	(26.1, 34.3)	29.4	(25.7, 33.8)	29.9	(26.3, 34.0)	98	(94, 102)	100	(96, 104)
AUC_{0-last} (ng*hr/mL)	1510	(1325, 1719)	1496	(1296, 1727)	1491	(1314, 1693)	99	(95, 104)	99	(95, 105)
$AUC_{0-\infty}$ (ng*hr/mL)	1519	(1334, 1730)	1508	(1307, 1740)	1501	(1323, 1703)	99	(95, 104)	100	(95, 104)
CL/F (L/hr)	32.9	(28.9, 37.5)	33.2	(28.7, 38.3)	33.3	(29.4, 37.8)	101	(96, 106)	101	(96, 105)
$T_{1/2}$ (hr)	50.7	(46.3, 55.5)	50.7	(45.7, 56.2)	50.8	(46.4, 55.7)	100	(96, 104)	101	(97, 105)
T_{max} (hr)	8.00	(8.00, 12.0)[b]	8.00	(8.00, 12.0)[b]	8.00	(8.00, 12.0)[b]	0.00	(-4.00, 4.00)[c]	0.00	(0.00, 4.00)[c]
SU012662										
C_{max} (ng/mL)	5.73	(4.83, 6.80)	5.39	(4.51, 6.45)	5.74	(4.84, 6.79)	93	(88, 98)	98	(93, 104)
AUC_{0-last} (ng*hr/mL)	665	(582, 759)	629	(543, 727)	658	(567, 763)	94	(89, 98)	98	(93, 103)
$AUC_{0-\infty}$ (ng*hr/mL)	684	(600, 781)	651	(564, 751)	677	(584, 785)	94	(90, 99)	98	(93, 102)
$T_{1/2}$ (hr)	87.3	(81.6, 93.5)	89.4	(83.0, 96.3)	87.4	(82.3, 92.8)	102	(100, 105)	100	(97, 102)
T_{max} (hr)	8.00	(4.00, 36.0)[b]	8.00	(2.00, 36.0)[b]	8.00	(4.00, 36.0)[b]	0.00	(-28.0, 24.0)[c]	0.00	(-32.0, 28.0)[c]

Source: A6181033 CSR, Table S2.

ANOVA = Analysis of Variance; AUC_{0-last} = Area Under Plasma Concentration Time Curve From 0 to Time of the Last Measurable Concentration; $AUC_{0-\infty}$ = Area Under Plasma Concentration Time Curve From 0 Extrapolated to Infinity; CL/F = Oral Clearance; C_{max} = Time to maximum concentration; CI = Confidence Interval; Geom. LS mean = Geometric Least Squares Mean; $T_{1/2}$ = Terminal Half-Life; T_{max} = Time to Maximum Concentration.

Treatment 1 = 50-mg clinical trial formulation of sunitinib (reference), Treatment 2 = 50-mg proposed commercial formulation of sunitinib (test).

Treatment 3 = Four × 12.5-mg proposed commercial formulation of sunitinib (test).

[a] Geometric least squares ratios and 90% CIs from ANOVA comparisons of test to reference treatments.

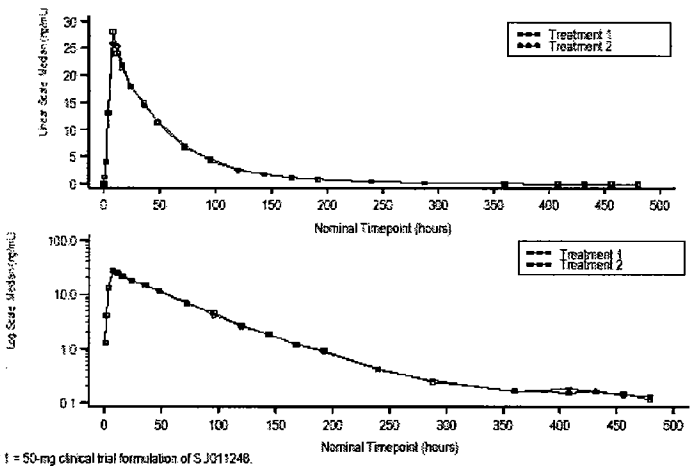
[b] Median (min, max).

[c] Median difference and range (in hours) from statistical comparison of Tmax using Hauschke, Steinijans, and Diletti's method.

A graphic representation of the data is presented below. Median plasma concentrations of SU01248, SU012662 and SU12448 from treatment 2and 3 are compared to treatment 1

Pfizer

Figure 14.2.1.1 - Median Plasma SU011248 Concentration vs. Time Profiles for Treatments 1 and 2
(Evaluable PK Population)

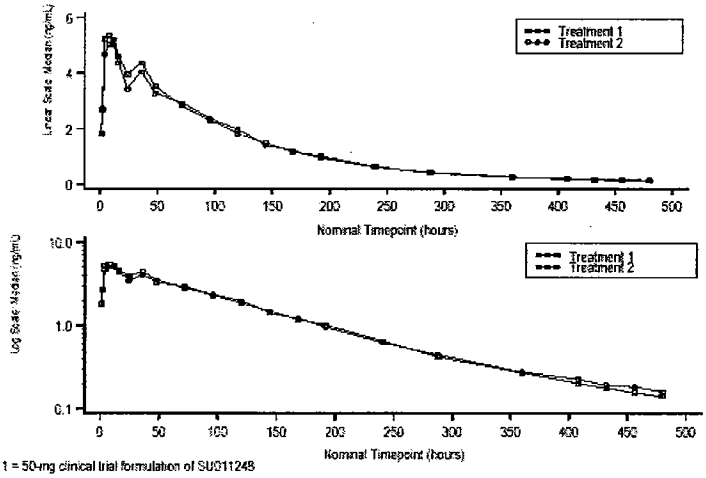


Treatment 1 = 50-mg clinical trial formulation of SJ011248.
Treatment 2 = 50-mg proposed commercial formulation of SU011248.
Reference: Table 13.5.1

Protocol A6181033 (Phase I Open-Label Study to Compare the PK of SU011248 in Healthy Subjects)
Program/Output (Date): F_PKMEDIAN/F_PKMEDIAN1.cgm (06APR05)

Pfizer

Figure 14.2.1.2 - Median Plasma SU012662 Concentration vs. Time Profiles for Treatments 1 and 2
(Evaluable PK Population)

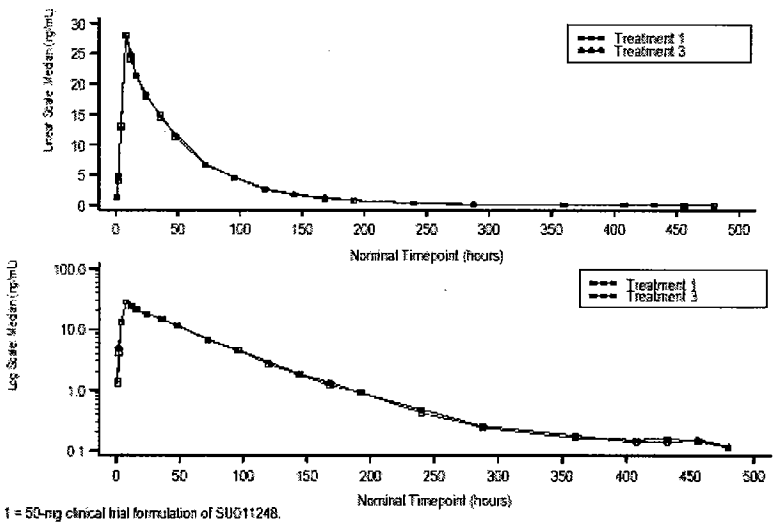


Treatment 1 = 50-mg clinical trial formulation of SU011248.
Treatment 2 = 50-mg proposed commercial formulation of SU011248.
Reference: Table 13.5.1

Protocol A6181033 (Phase I Open-Label Study to Compare the PK of SU011248 in Healthy Subjects)
Program/Output (Date): F_PKMEDIAN/F_PKMEDIAN1.cgm (06APR05)

Pfizer

Figure 14.2.2.1 - Median Plasma SU011248 Concentration vs. Time Profiles for Treatments 1 and 3
(Evaluable PK Population)

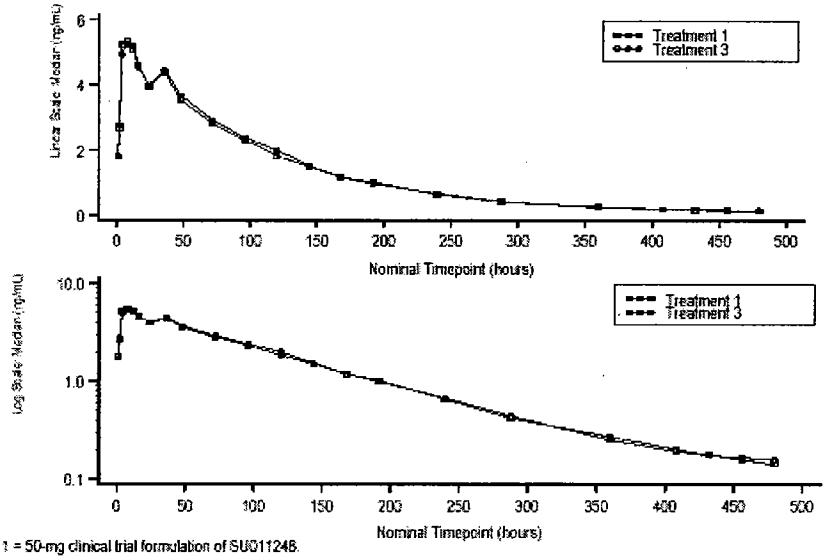


Treatment 1 = 50-mg clinical trial formulation of SU011248.
Treatment 3 = Four X 12.5-mg proposed commercial formulation of SU011248.
Reference: Table 13.5.1

Protocol A6181033 (Phase I Open-Label Study to Compare the PK of SU011248 in Healthy Subjects)
Program/Output (Date): F_PKMEDIAN/F_PKMEDIAN1.cgm (06APR05)

Pfizer

Figure 14.2.2.2 - Median Plasma SU012662 Concentration vs. Time Profiles for Treatments 1 and 3
(Evaluable PK Population)



Treatment 1 = 50-mg clinical trial formulation of SU011248.
Treatment 3 = Four X 12.5-mg proposed commercial formulation of SU011248.
Reference: Table 13.5.1

Protocol A6181033 (Phase I Open-Label Study to Compare the PK of SU011248 in Healthy Subjects)
Program/Output (Date): F_PKMEDIAN/F_PKMEDIAN1.cgm (06APR05)

Multiple peaks were observed in SU012662 plasma concentrations for some subjects, resulting in some variability in Tmax estimates for this analyte (range of 2 to 36 hours). However, this occurrence did not have any impact on the results of this study since statistical comparisons showed no difference in SU012662 Tmax between treatments, and the geometric least squares mean ratios and 90% CI for comparisons of all other SU012662 parameters (Treatment 2/Treatment 1 and Treatment 3/Treatment 1) fell within the 80% to 125% bioequivalence criteria. Additionally, since all SU011248 parameters, including Cmax, were bioequivalent for both treatment comparisons, and there was no difference in SU011248 Tmax between treatments, the multiple SU012662 peaks and variable Tmax values observed were not due to differences in SU011248 absorption between treatments.

CONCLUSIONS

The results of this study demonstrate that the 50-mg proposed commercial formulation (Treatment 2; test) and 4 x 12.5-mg proposed commercial formulation (Treatment 3; test) are both bioequivalent to the 50-mg clinical trial formulation (Treatment 1; reference). The geometric least squares mean ratios and 90% CI for all primary PK parameters (SU011248 AUC0-last, AUC0-∞, and Cmax) and all secondary parameters fell within the 80% to 125% acceptance criterion used for establishing bioequivalence, for both treatment comparisons (Treatment 2/Treatment 1 and Treatment 3/Treatment 1). Tmax for both analytes was comparable between formulations. The geometric mean half-lives of SU011248 and SU012662 in this study were approximately 51 hours and 88 hours, respectively. PK blood collections up to 480 hours postdose, done for this study, were sufficient to estimate half-lives since this sampling time is about 9 and 5 times the terminal half-lives of SU011248 and SU012662, respectively. There were no unexpected safety concerns on any of the 3 treatments; the safety results were similar between treatments. The SU011248 50-mg proposed commercial formulation (test) and 4 x 12.5-mg proposed commercial formulation (test) are both bioequivalent to the 50-mg clinical trial formulation (reference).

B.3. Study A6181046

Title: Phase 1 Open-Label Study to Compare the Pharmacokinetics of SU011248 Administered as Clinical Trial 12.5-mg Capsules and Proposed Commercial 12.5-mg Capsules Healthy Subjects

Investigators: [redacted]

Dates: 11 October 2004 to 20 December 2004

Objective(s): To establish the bioequivalence of the proposed commercial 12.5-mg SU011248 capsule to the clinical trial 12.5-mg SU011248 capsule.

Study Design: This trial was an open-label, randomized, single-dose, 2-treatment (proposed commercial formulation vs. clinical trial formulation), 2-way crossover study in healthy subjects.

Treatment:

Sixteen subjects enrolled in the study and comprised the safety analysis population. Eight subjects (50%) were treated in Treatment Sequence 1-2 and 8 were treated in Treatment Sequence 2-1. All 16 subjects (100%) had at least 1 calculable PK parameter and were included in the evaluable population. All subjects (100%) completed the study per protocol. SU011248 L-malate salt was provided as outlined in Table B.3.1.

Table B.3.1: Lot Numbers

Study Drugs and Lot Numbers			
Study Drug	**Dosage form**	**Lot number**	**Particle size**
Clinical trial (TRT 1)	12.5 mg sunitinib malate capsule	N0400277	
Proposed Commercial (TRT 2)	12.5 mg sunitinib malate capsule	N0400280	

Sample Collection:
During all treatment periods, blood samples (4 mL), to provide a minimum of 2 mL plasma for PK analysis, were collected into appropriately labeled tubes containing K2EDTA. PK collections were performed at the following timepoints:
Hour 0 (pre-dose), Hours 1, 2, 4, 8, 12, 16 (Day 1), Hours 24, 36 (Day 2), Hour 48 (Day 3), Hour 72 (Day 4), Hour 96 (Day 5), Hour 120 (Day 6), Hour 144 (Day 7), Hour 168 (Day 8), Hour 192 (Day 9), Hour 240 (Day 11), Hour 288 (Day 13), Hour 360 (Day 16), Hour 408 (Day 18), Hour 432 (Day 19), Hour 456 (Day 20), and Hour 480 (Day 21) post-dose.

Safety Evaluations: Adverse events were summarized and reported to the sponsor on an ongoing basis during the study to evaluate the safety. Other parameters such as electrocardiogram, physical examination, blood pressure, pulse rate, safety laboratory data, medical history and concomitant medications were reviewed and summarized by the investigator. Any abnormalities of potential clinical significance were assessed by the investigator and reported to the sponsor. Safety data are presented in tabular and/or graphical format and summarized descriptively.

There was 1 clinically significant (grade 3 or 4) adverse event. Subject A6181046-121110-00020 experienced a grade 3 headache, which was not related to treatment and resolved without treatment in one day. There were no deaths and no serious adverse events. No subjects discontinued or had a dose delay or change. All adverse events resolved without treatment because of adverse events.

Analytical Method Performance:
Human K3EDTA plasma samples were assayed for the determination of SU011248 and SU012662 concentrations using a validated, sensitive and specific isocratic liquid chromatographic tandem mass spectrometric (LC/MS/MS) method in the positive ionization mode. The analytical method performance parameters are shown in table B.3.2.

Table B.3.2. Assay Performance for Study A6181046

Dates of Analysis		August 2, 2001 to August 8, 2001		
		SU011248	SU012662	SU012487
Matrix		Plasma	Plasma	Plasma
Specificity	Chromatogram	Specific for sunitinib	Specific for SU012662	Specific for SU012487
Linearity	Correlation Coefficient	0.998100	0.99888	0.99704
Reproducibility standard)(n=8)	inter- run %CV 0.1 ng/mL – 100 ng/mL	1.8 to 10.8%	3.3% - 5.2%	5.5%-8.7%
%Accuracy (Standards) n=8	0.3-80 ng/mL	98.4%-108.5%	99.1%-108.12%	97.4%-102.0%
Interassay Precision QC samples (n=24)	Inter-run (0.3-80 ng/mL)	2.5% - 7.2%	4.3% - 8.4%	7.6%-11.6%
Inter assay Accuracy QC samples (n=24)	Inter-run 0.3 ng/mL -100 ng/mL	99.3%-102.1%	102.0%-102.9%	99.0%-101.6%

Pharmacokinetics: The following parameters were calculated for SU011248 and its metabolite, SU012662: Cmax, Tmax, AUC0-last (area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration), AUC0-∞, t1/2 (half-life), AUC0-24, AUC0-72, and CL/F (oral

clearance, calculated for SU011248 only). Plasma PK parameter values were calculated by noncompartmental analysis of concentration-time data using WinNonlin Version 3.2. Actual sample collection times were used for PK analysis. All concentrations assayed as below the limit of quantification (BLQ) were set to zero.

Statistical Methods: All PK parameters for SU011248 and SU012662 were listed and summarized by treatment using descriptive statistics. Subjects who had PK parameters for at least one treatment were included in the statistical comparisons of PK parameters. A linear mixed-effects statistical model, which included factors accounting for the sources of variation, sequence, subject nested in sequence, period, and treatment, was fit to each log-transformed PK parameter. The difference in the means of each log-transformed pharmacokinetic parameter (test – reference) and 90% confidence intervals (CI) on this difference were calculated, and then back-transformed to obtain the ratio of the geometric least squares means and corresponding 90% CI for that parameter. Median values and ranges were presented for Tmax. The analysis of Tmax followed the nonparametric Hauschke, Steinjans, and Diletti procedure. First, within each sequence and for each subject, the difference in Tmax between the 2 periods was calculated. Next, all possible pairwise combinations of observed differences between the first sequence and second sequence were created (eg. Subject X, from Sequence 1-2, their difference in Tmax is paired with every subject's recorded difference in Sequence 2-1). Finally, the difference in the differences between sequences is calculated and the median, minimum, and maximum values were reported.

RESULTS

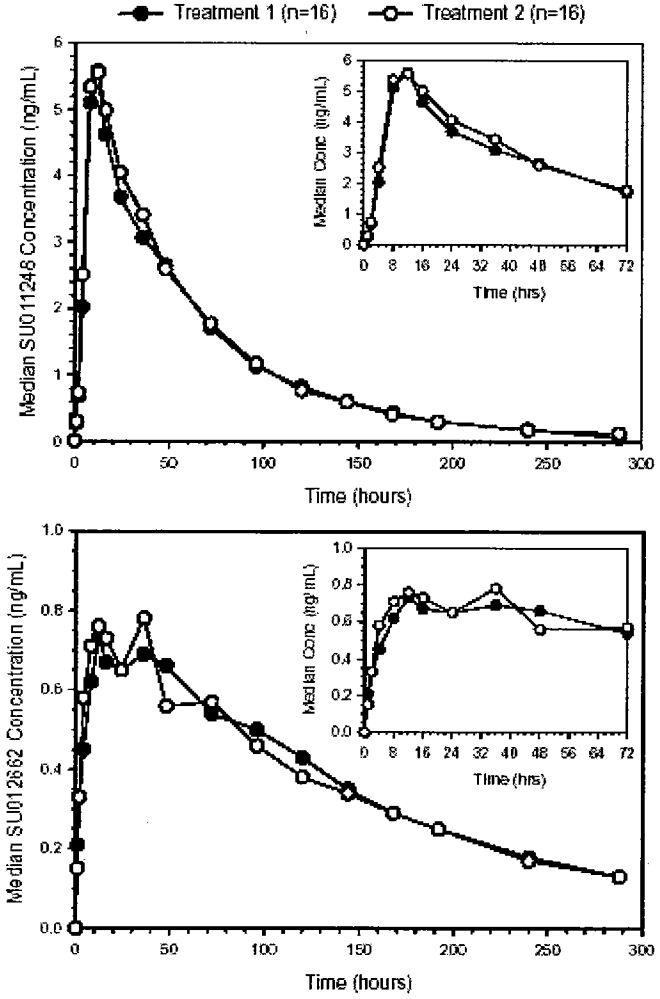
Pharmacokinetic Results: Table B.3.3 below summarizes SU011248 and SU012662 PK parameters for each treatment, and the results of statistical comparisons between treatments.

Table B.3. 5: Summary of SU011248 and SU012662 PK Parameters for 12.5 mg SU011248 Clinical Trial and Proposed Commercial Formulations and Results of Statistical Comparisons Between Formulations

Parameter	Geometric Mean (95% CI)		Statistical Comparison (Treatment 2/1) [a]	
	Treatment 1 (n=16)	Treatment 2 (n=16)	Geom. LS Mean Ratio (%)	90% CI (%)
PRIMARY PK PARAMETERS				
SU011248				
C_{max} (ng/mL)	5.56 (4.81, 6.42)	5.44 (4.74, 6.25)	98	94, 102
$AUC_{0\text{-}last}$ (ng*hr/mL)	335 (296, 380)	334 (294, 381)	100	96, 103
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	346 (307, 391)	345 (304, 392)	100	96, 103
SECONDARY PK PARAMETERS				
SU011248				
$AUC_{0\text{-}24}$ (ng*hr/mL)	93.4 (81.9, 107)	94.5 (83.2, 107)	101	98, 104
$AUC_{0\text{-}72}$ (ng*hr/mL)	219 (196, 245)	222 (198, 248)	101	98, 105
CL/F (L/hr)	36.1 (32.0, 40.8)	36.2 (31.9, 41.1)	100	97, 104
$t_{1/2}$ (hr)	54.5 (49.4, 60.3)	52.5 (46.6, 59.1)	96	90, 102
T_{max} (hr)	12.0 (8.00, 16.0) [b]	12.0 (8.00, 16.0) [b]	0.00 [c]	-4.00, 4.02 [c]
SU012662				
C_{max} (ng/mL)	0.78 (0.68, 0.89)	0.82 (0.70, 0.95)	105	99, 112
$AUC_{0\text{-}last}$ (ng*hr/mL)	113 (101, 126)	115 (97.5, 137)	102	95, 110
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	132 (119, 147)	136 (117, 157)	102	97, 109
$AUC_{0\text{-}24}$ (ng*hr/mL)	13.9 (11.8, 16.5)	14.8 (12.5, 17.5)	106	98, 115
$AUC_{0\text{-}72}$ (ng*hr/mL)	44.2 (39.2, 49.9)	46.7 (40.3, 54.1)	105	99, 113
$t_{1/2}$ (hr)	104 (90.1, 120)	103 (88.6, 119)	99	93, 105
T_{max} (hr)	18.0 (2.10, 144) [b]	26.0 (4.00, 72.0) [b]	-0.01 [c]	-53.0, 34.0 [c]

Geom. LS mean – geometric least squares mean; CI – confidence interval.
Treatment 1 – 12.5 mg clinical trial formulation of SU011248; Treatment 2 - 12.5 mg commercial formulation of SU011248.
a Geometric least squares ratio and 90% CIs from mixed effects model comparing Treatment 2 (test) to Treatment 1 (reference).
b Median (min, max).
c Median difference and range from statistical comparison of T_{max} using Hauschke, Steinijans, and Diletti's method.

Figure 1. Linear Plots of Median Plasma SU011248 and SU012662 Concentration-time Profiles in Healthy Subjects Following Treatment with the 12.5 mg SU011248 Clinical Trial and Proposed Commercial Formulations



Note: Treatment 1 = 12.5 mg clinical trial formulation of SU011248 (reference); Treatment 2 = 12.5 mg proposed commercial formulation of SU011248 (test). The inset plots show an expanded view of the 0 - 72 hour time period. Median concentrations beyond 288 hours are not shown because concentrations were BLQ (< 0.1 ng/mL) for both analytes.

The results of this study indicate that the 12.5 mg proposed commercial formulation (Treatment 2) is bioequivalent to the 12.5 mg clinical trial formulation (Treatment 1). Geometric least squares mean ratios (Treatment 2/Treatment 1; expressed as a percentage) for the primary PK parameters, SU011248 Cmax, AUC0-last, and AUC0-inf. were close to or equal to 100% and the 90% CIs on these ratios were well within the 80% to 125% acceptance limits for bioequivalence. The 90% CIs for all secondary SU011248 and SU012662 PK parameters analyzed using ANOVA also fell within this 80% to 125% bioequivalence limits. No difference was observed in SU011248 Tmax between treatments. In the case of SU012662, only a negligible difference (-0.01 hour median difference) was observed in SU012662 Tmax between treatments.

SU011248 and SU012662 half-lives were estimable for all subjects and treatments. Geometric mean half-lives were about 53 to 55 hours for SU011248, and 103 to 104 hours for SU012662. Intersubject

variability was moderate, with CV% (based on arithmetic means and STDs) for Cmax, AUC0-last, and AUC0-inf., ranging from 22 to 25% for SU011248 and 21 to 33% for SU012662 across both treatments. Intersubject CV%s for Cmax, AUC0-last, and AUC0-inf., estimated from the statistical model were 22 to 26% for SU011248 and 24 to 26% for SU012662, which were generally similar to the values estimated from arithmetic means and STDs. Intrasubject variability, also estimated from the statistical model, was low, with CV%s for Cmax, AUC0-last, and AUC0-inf., ranging from 5.7 to 6.4% for SU011248 and 9.7 to 11.9% for SU012662.

Conclusion(s): The results of this study demonstrate that the proposed 12.5 mg commercial formulation (Treatment 2; test) is bioequivalent to the 12.5 mg clinical trial formulation (Treatment 1; reference). The geometric least squares mean ratios and 90% CI for all primary PK parameters (SU011248 AUC0-last (96-103%), AUC0-inf. (96%-103%), and Cmax (945-102%) and secondary parameters fell within the 80% to 125% acceptance criterion used for establishing bioequivalence. Tmax for both analytes was comparable between formulations. Results of safety laboratory assessments, vital signs assessments, and electrocardiogram assessments did not indicate any unexpected risks of SU011248 in either the clinical or proposed commercial formulation.

C. ANALYTICAL METHOD VALIDATION REPORT: SUNITINIB IN PLASMA

SUMMARY

[ ] has validated [ ] method for the determination of SU011248, SU012662, and SU012487 in K3EDTA human plasma. The new procedure, #820-0499, is entitled "SU011248, SU012662, and SU012487 in K3EDTA Human Plasma." The method's performance during the validation exercise is outlined in this report.

Method Summary

Samples were collected, mixed with anticoagulant, and then placed immediately into an ice bath or cryoblock to ensure that samples were kept at 2° to 8 °C during harvesting to minimize exposure to light. Plasma samples were immediately stored at –20 °C within 30 minutes. SU011248 and SU012662 were extracted from human plasma [ ] at alkaline pH with ethyl acetate in a 96-well plate. Before extraction, a deuterated internal standard of SU011248 was added. [

]

VALIDATION STUDY

In summary, batch calibration requires a minimum of 8 single standard concentrations or 6 standards in duplicate. Three concentrations of Quality Control (QC) samples as well as blank samples are also included in each run, with 6 replicates of each QC in at least three batches. Standards are dropped from the regression set such that no point can remain in the curve with a bias in the back-calculated concentration greater than ±20%, and a minimum of — of the original calibration standards must remain in the final curve.

Stability samples are subjected to freeze/thaw, room temperature, and long-term frozen storage conditions. The same precision and accuracy criteria are applied to these sample results. Analyses of separate pools at the upper and lower limits of quantitation are also evaluated for precision and accuracy.

TABLE 2. SCHEDULE OF BATCHES ASSAYED

Batch	Date Extracted	Content
D03O	2-Aug-01	Intra-assay Precision and Accuracy
D04O	3-Aug-01	Intra-assay Precision and Accuracy, Specificity, Upper Limit of Quantitation, Lower Limit of Quantitation, Dilution Integrity
D05O	6-Aug-01	Intra-assay Precision and Accuracy, Recovery, Stability in Matrix, Extract Stability [ ] Freeze-Thaw Stability
D06O	8-Aug-01	Extract Stability (SU012487 only-[ ]

D01O and D02O were method development batches.

TABLE 3. REFERENCE STANDARD INFORMATION

Compound	Lot	Source
SU011248	002103	Sugen
SU012662	002108	Sugen
SU012487	002112	Sugen
[$^{2}H_{10}$]SU011248	53/48	Sugen

RESULTS AND DISCUSSION

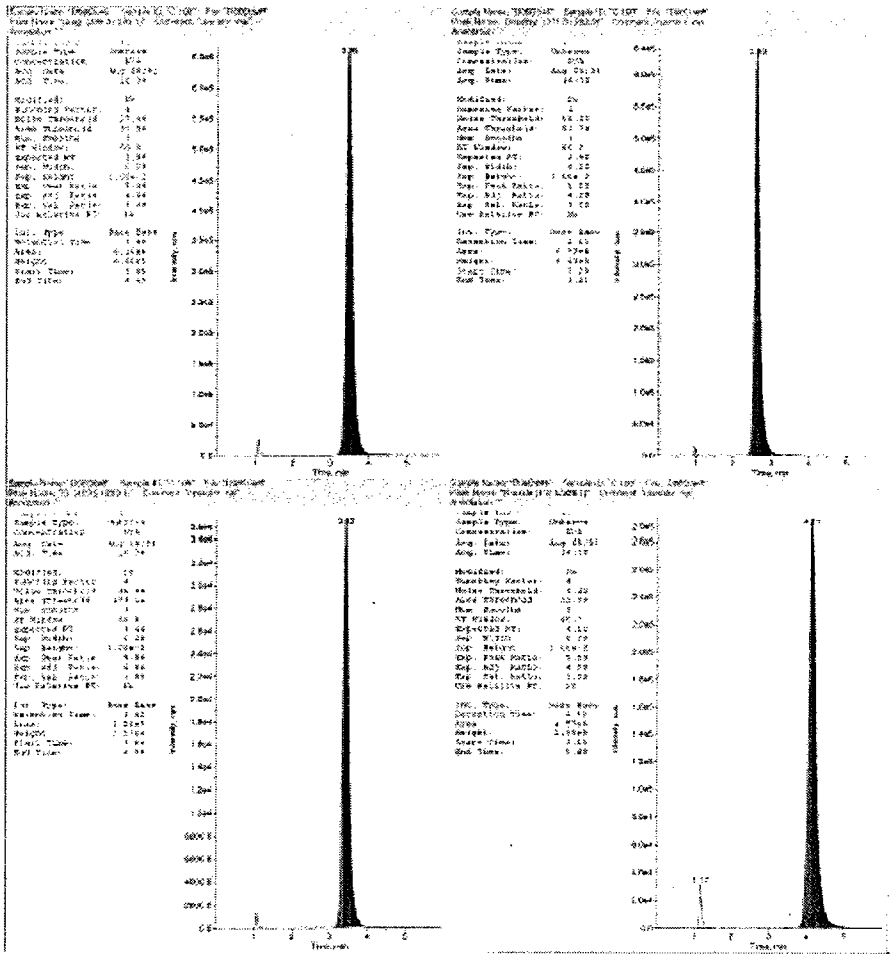
A summary of the performance parameters are given in the following table.

Analytical Method Performance				
		SU011248	SU012662	SU01287
Matrix		Plasma	Plasma	Plasma
Method		LC/MS/MS	LC/MS/MS	LC/MS/MS
Analysis dates	Aug -2-01 to Aug-8-01			
Calibration curve	0.1-100 ng/mL	SU011248	SU012662	SU012487
Precision	100 ng/mL	1.8%	4.5%	5.5%
Standards	80 ng/mL	1.5%	3.5%	7.0%
	25 ng/mL	1.7%	3.3%	6.4%
	5 ng/mL	1.8%	4.2%	6.7%
	0.30 ng/mL	7.4%	4.9%	6.6%
	0.10 ng/mL	10.8%	5.2%	8.7%
Accuracy	100 ng/mL	101.4%	100.8%	102.3%
Standards	80 ng/mL	99.0%	99.1%	97.4%
	25 ng/mL	99.5%	99.2%	98.0%
	5 ng/mL	101.2%	101.1%	101.0%
	0.30 ng/mL	98.4%	99.7%	102.0%
	0.10 ng/mL	108.5%	108.1%	99.1%

Analytical Method Performance				
		SU011248	SU012662	SU01287
Correlation coefficient	N=4	0.99810	0.99888	0.99704
Intra-assay	80 ng/mL	5.5%	6.7%	9.6%
Precision	40 ng/mL	0.5%	3.8%	1.2%
N=24	0.300	4.8%	5.2%	4.1%
QC samples	80 ng/mL	3.0%	2.6%	4.2%
	40 ng/mL	0.5%	3.4%	10.0%
	0.300	2.7%	5.5%	13.6%
	80 ng/mL	3.3%	3.9%	3.4%
	40 ng/mL	2.4%	3.5%	4.1%
	0.300	4.5%	5.2%	2.4%
Intra-assay	80 ng/mL	102.4%	92.7%	87.1%
Accuracy	40 ng/mL	98.0%	97.0%	92.9%
N=24	0.300	97.0%	96.9%	89.6%
QC samples	80 ng/mL	108.4%	106.3%	109.5%
	40 ng/mL	98.7%	106.3%	104.7%
	0.300	101.7%	107.3%	101.7%
	80 ng/mL	104.5%	108.6%	108.0%
	40 ng/mL	100.1%	100.9%	106.7%
	0.300	96.5%	97.8%	103.7%
Inter-assay	80 ng/mL	3.8%	8.0%	10.2%
Precision	40 ng/mL	2.4%	5.1%	7.6%
N=24	0.300	4.3%	6.7%	11.6%
Inter-assay	80 ng/mL	102.1%	102.4%	101.4%
Accuracy	40 ng/mL	99.9%	102.9%	101.6%
N=24	0.300	99.3%	102.0%	99.0%
Limits of Quantitation	Lower	0.100 ng/mL	0.100 ng/mL	0.100 ng/mL
	Upper	100 ng/mL	100 ng/mL	100 ng/mL
Specificity	6 lots of matrix	No greater than 5%	No greater than 5%	No greater than 5%
Extract Stability	QC samples RT/dark — hours	Met precision and accuracy criteria	Met precision and accuracy criteria	Met precision and accuracy criteria
	Freeze/Thaw -20°C for — cycles	Met precision and accuracy criteria	Met precision and accuracy criteria	Met precision and accuracy criteria
Stock Standard Stability	4°C for — days	Met % difference criteria	Met % difference criteria	Met % difference criteria

FIGURE 1. CHROMATOGRAM OF HIGH CALIBRATION STANDARD[1]

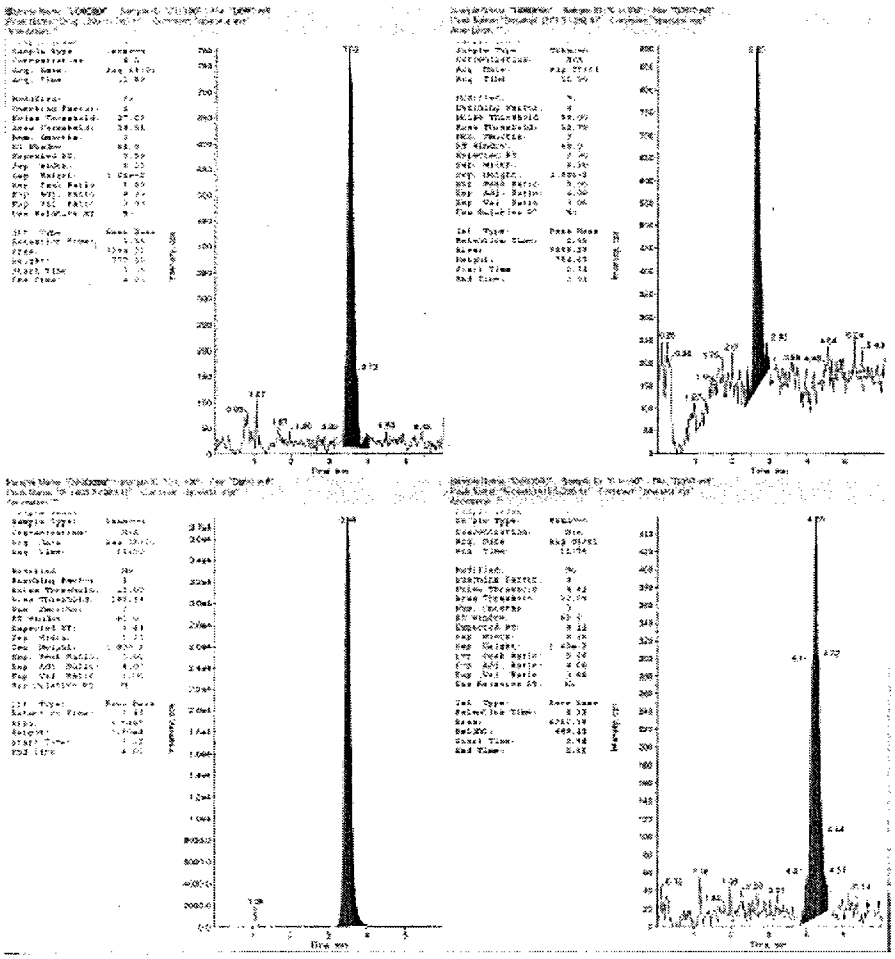
Batch D06O, Run 45



[1] In the chromatograms presented in Figures 1 - 3, from left to right, the upper row represents SU011248 and SU012662 and the lower row represents the internal standard and SU012487.

FIGURE 2. CHROMATOGRAM OF LOW CALIBRATION STANDARD

Batch D06O, Run 6



D. DISSOLUTION METHOD DEVELOPMENT

During development of the dissolution method the following parameters have been evaluated:

- [illegible]
- [illegible]
- [illegible]
- [illegible]

Selection of Apparatus

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____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

The firm bases the proposed acceptance criterion of[ ] dissolved (Q =[ ], at 30 minutes on the release and stability data for batches of sunitinib malate capsules used in clinical studies throughout development. The acceptance criterion has also been set taking into account the data generated through development and robustness testing of the commercial formulation and commercial manufacturing process, which showed consistent and reproducible dissolution performance. Capsules on long term and accelerated stability have continued to meet this criterion.

Comments:
The aqueous solubility and permeability data submitted by the firm indicate the product is a Class 4 under the Biopharmaceutics Classification System with low solubility and low permeability. Based on the

information provided in during the development of a dissolution procedure, the following information has been determined:

- [redacted]

The studies have demonstrated the dissolution method for the testing of sunitinib malate capsules using USP II paddle apparatus rotating at [redacted] rpm in 900 mL of hydrochloric acid (0.1 M) held at 37°C ± 0.5°C is suitable for assessing capsule performance. The proposed method is acceptable. Based on the data submitted, a tolerance specification of Q=[redacted] at 30 minutes appears to be an acceptable tolerance specification.

Recommendation:
The dissolution method proposed by the firm is acceptable. The product will meet a tolerance specification of Q=[redacted] at 30 minutes. The recommended dissolution procedure is:

Apparatus:	Apparatus 2, Paddle Method
Rotation Speed:	[redacted] rpm
Medium:	0.1M HCl
Volume:	900 mL
Analytical:	UV Spectroscopy
Tolerance:	Q=[redacted] at 30 minutes

Dissolution Analytical Method Validation:
The method was validated in accordance with ICH Q2B guideline. A summary of the methods used and the results are presented below:

Table 1: Method Validation: Determination of the Dissolution of SU011248 from Sunitinib Malate by Ultraviolet Spectroscopy

Specificity	Specific for Sunitinib Malate			
Linearity	[redacted]			
Accuracy of LC)				
Precision				
Intermediate Precision				

	Overall %Relative Standard Deviation		
Stability	Initial		
	After — RT (protected from light)		
	After — 5°C (Protected from light)		

Comment
The analytical method is acceptable based on the information submitted by the firm.

Comparison of Automated and Manual Dissolution
The dissolution testing of sunitinib malate capsules may be performed either manually or using an automated dissolution system. The dissolution of a batch of 12.5 mg and 50 mg capsules (N = 12) was performed using [ ] automated [ ] dissolution system and also manually with — UV analysis. The data are presented in Table 2 (12.5 mg capsule) and Table 3 (50 mg capsule) and confirm the equivalence of both the automated and manual methods of dissolution testing.

Table 2: 12. 5 mg Capsules

Sample	Manual % Dissolution 15 minutes	Manual % Dissolution 30 minutes	Automated % Dissolution 15 minutes	Automated % Dissolution 30 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	102	102	101	102
% Relative Standard Deviation	0.6	1.3	2.7	2.2

Table 3: 50 mg Capsules

Sample	Manual % Dissolution 15 minutes	Manual % Dissolution 30 minutes	Automated % Dissolution 15 minutes	Automated % Dissolution 30 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	98	99	99	99
% Relative Standard Deviation	2.6	2.2	2.7	2.4

Comment:
The information submitted by the firm indicates that the automated dissolution procedure is comparable to the manual dissolution procedure.

Stability Data to Support Tolerance Specification

The following clinical and primary stability batches (Table 4) manufactured using the commercial formulation at Nerviano Medical Sciences in Nerviano, Italy were tested using the dissolution procedure selected by the firm. The results are only given at the 30 minute time point. The firm has proposed a specification of Q=

Table 4: Clinical and Primary Stability Batches Manufactured using the Commercial Formulation at Nerviano Medical Sciences Dissolution Results at 30 minutes

Batch Number	# of Capsules	Strength	Mean	Range	%RSD
N0400280		12.5 mg	102		1.2
N0400282		12.5 mg	104		1.4
N0400283		12.5 mg	103		1.4
N0401059		12.5 mg	104		1.6
N0401060		12.5 mg	104		1.4
N0401287		12.5 mg	103		1.5
N0400284		25 mg	99		2.0
N0400285		25 mg	97		1.3
N0400286		25 mg	97		1.7
N0401064		25 mg	97		2.3
N0401062		25 mg	97		1.9
N0400287		50 mg	103		1.9
N0400288		50 mg	99		2.0

N0400289	50 mg	99	1.7
N0401067	50 mg	102	1.5
N0401068	50 mg	102	1.5
N0401069	50 mg	101	1.6

Stress Conditions Stability

Stability under stress storage conditions was conducted by placing samples of primary stability batches N0400542, N0400546 and N0400495 on storage at 25°C/80% RH for [ ] and at 50°C for [ ] s. No significant changes were observed and therefore it is concluded that sunitinib malate capsules are stable at 25°C/80% RH for [ ] and at 50°C for [ ]

Photostability

Photostability was conducted by placing samples of primary stability batches N0400542, N0400546 and N0400495 directly exposed to ICH photostability conditions (Q1B). No significant changes were observed , therefore it is concluded that sunitinib malate in capsules is stable to light and no precautionary packaging or labeling is required.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

E. WAIVER REQUEST

A waiver of the in vivo bioequivalence data necessary for the approval of the 25-mg strength sunitinib malate capsule was granted based on linear pharmacokinetic performance across the strengths to-be-marketed, the high solubility across the pH range of pH 1.2 to pH 6.8, and the in vitro dissolution comparison of the profiles generated for three 25-mg commercial batches and the 50-mg clinical trial formulation using the following dissolution procedure:

Apparatus:	USP Apparatus II (Paddle Method)
Rotation Speed:	~ rpm
Medium:	0.1M HCl
Volume:	900 mL
Analytical:	UV Spectroscopy

Dissolution performance of the product was found to be comparable and across the media (pH 1.2 – pH 6.8). The profiles for all three capsule strengths are presented in Figure 1 (0.1M HCl), Figure 2 (pH 6.8 Phosphate Buffer) and Figure 3 (pH 4.5 Acetate Buffer).

Figure 1. Dissolution Profiles of Sunitinib Malate Capsules in 0.1M Hydrochloric Acid with Paddles at ~ rpm

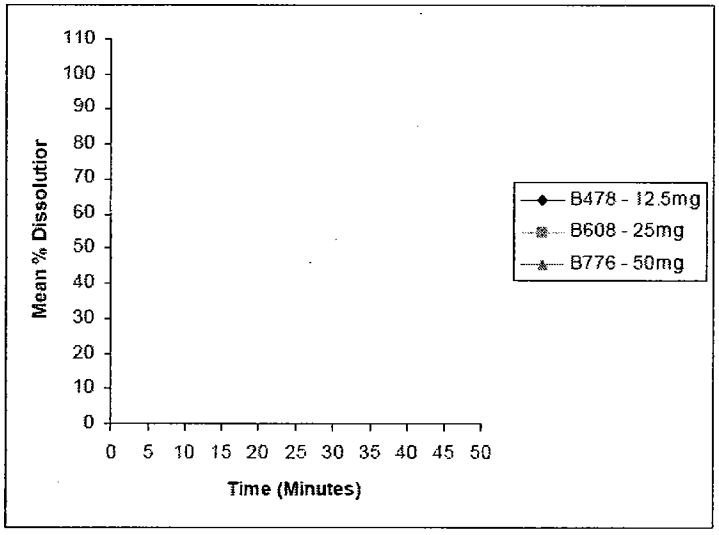


Figure 2. Dissolution Profiles of Sunitinib Malate Capsules in pH 6.8 Buffer with Paddles at rpm

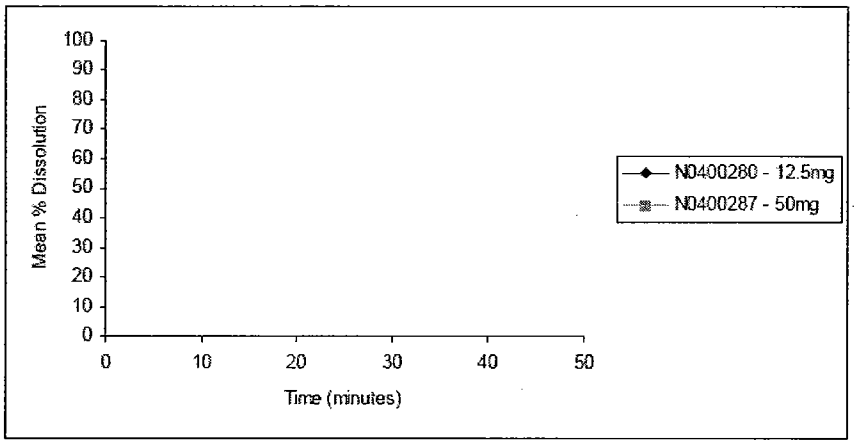
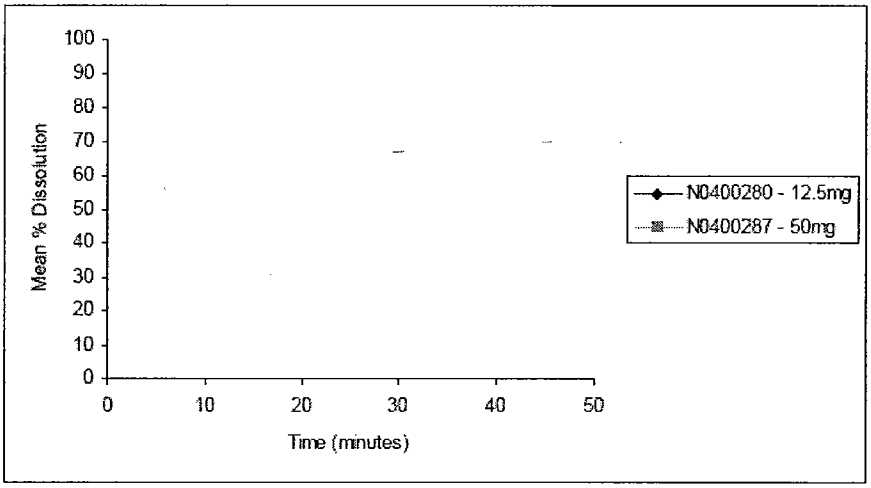


Figure 3. Dissolution Profiles of Sunitinib Malate Capsules in pH 4.5 Buffer with Paddles at rpm



Note: batches N0400280 and N0400287 were used in bioequivalence studies

Dissolution data for three batches each of 25 mg and 50 mg sunitinib malate capsules manufactured at Pfizer Ascoli and one batch of each dosage strength manufactured at Nerviano Medical Sciences are used to evaluate the comparability of the dissolution profiles in 0.1M HCl. The following batches were used in this study:

Lots used in Waiver Request		
Batch	Strength	Manufacture location
B608	25 mg	Ascoli

B 724	25 mg	Ascoli
B 725	25 mg	Ascoli
N 0400286	25 mg	Nerviano
B776	50 mg	Ascoli
B792	50 mg	Ascoli
B 829	50 mg	Ascoli
N0400827	50 mg	Nerviano

Twelve unit profiles were generated for each batch. A summary of the results are presented in the following table.

Batch	Strength	5 min	10 min	15 min	20 min	30 min	45 min	F2 (all)	F2 (5-20)
B608	25 mg	[redacted]						64.7	64.7
B724	25 mg							64.7	60.6
B725	25 mg							81.8	84.9
N0400286	25 mg							90.1	91.6
B776	50 mg							56.8	57.1
B792	50 mg							43.3	43.3
B829	50 mg							54.1	54.2
N0400827	50 mg							Reference	

The batches showed significant variability in the dissolution results at 5 minutes (% relative standard deviation >20%). The f2 similarity factor was calculated using the dissolution results from all time points and from the 5, 10, 15 and 20 minute checkpoints. The results using 50 mg batch N0400827 (used in a BE study) as the reference lot, indicated that the 25 mg lots have comparable dissolution profiles. Furthermore, the dissolution performance was observed to be rapid [redacted] release in 15 minutes). The raw data are provided in the following tables.

25 mg Capsules	B608 - Pfizer Ascoli						B724 - Pfizer Ascoli						B725 - Pfizer Ascoli						N0400286 -Nerviano					
Capsule Number/ Timepoint	5'	10'	15'	20'	30'	45'	5'	10'	15'	20'	30'	45'	5'	10'	15'	20'	30'	45'	5'	10'	15'	20'	30'	45'
1																								
2																								
3																								
4																								
5																								
6																								
7																								
8																								
9																								
10																								
11																								
12																								
Mean	83	99	102	102	102	102	80	98	100	100	100	100	95	100	101	101	101	101	80	94	98	98	98	98
Minimum																								
Maximum																								
% RSD	29.3	6.5	1.2	1.3	1.2	1.4	33.4	7.3	1.9	1.9	1.9	1.9	12.7	1.7	1.7	1.8	2.1	1.9	32.2	10.6	1.7	1.5	1.3	1.5

50 mg Capsules	B776 - Pfizer Ascoli						B792 - Pfizer Ascoli						B829 - Pfizer Ascoli						N0400287 -Nerviano					
Capsule Number/ Timepoint	5'	10'	15'	20'	30'	45'	5'	10'	15'	20'	30'	45'	5'	10'	15'	20'	30'	45'	5'	10'	15'	20'	30'	45'
1	[redacted]																							
2																								
3																								
4																								
5																								
6																								
7																								
8																								
9																								
10																								
11																								
12																								
Mean	70	95	98	100	101	101	59	95	98	98	99	99	72	98	100	100	100	100	92	99	99	99	99	99
Minimum	[redacted]																							
Maximum	[redacted]																							
% RSD	48.7	19.9	8.7	3.6	1.5	1.4	44.0	5.2	2.1	1.6	1.6	1.5	26.7	3.3	1.4	1.4	1.4	1.4	13.6	3.3	1.0	1.2	1.2	1.4

5. PHARMACOMETRICS REVIEW

SUMMARY

The applicant has conducted an extensive population pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) analysis with the following objectives: 1) To describe sunitinib and SU012662 (the primary equipotent metabolite) PK following single and multiple dose administration of sunitinib in healthy subjects and patients, 2) To identify covariates that are important determinants of sunitinib and SU012662 disposition, 3) To characterize the exposure-response relationships for effectiveness (objective response rate, time to tumor progression) and tolerability using nonlinear mixed effects modeling, and 2) To identify factors that affect sunitinib response in the solid tumor, GIST, and MRCC patient populations.

Pharmacokinetic Modeling

- A population PK model was developed to describe sunitinib and SU012662 pharmacokinetics (PK) following single and multiple dose administration of sunitinib. PK data was combined from 13 studies in healthy subjects and patients with GIST, MRCC, solid tumors and AML. Models were developed to identify significant covariates of clearance and volume of distribution of sunitinib and SU012662.
- The final model indicated significant effects of sex, tumor type on the clearance of sunitinib and significant effects of sex, weight, tumor type, on the clearance of the metabolite. Significant effects were obtained for age, tumor type, weight, gender on Vd/F of sunitinib as well as SU012662.
- However, inclusion of the covariates did not result in an appreciable reduction in inter-individual variability in clearance or volume of distribution. Inclusion of covariates reduced the IIV in clearance of SU011248 from 42% to 37% and IIV in clearance of SU012662 from 46% to 38%. This indicates that the covariates included in the models did not improve the predictability of the model.

Exposure-Response for Effectiveness – Sponsor's Analysis

- The applicant's E-R analysis focused on time to tumor progression or death (TTPD) and objective response rates. TTPD was modeled using parametric time-to-event (survival) analysis. Objective response rate was modeled using repeated measures logistic regression.
- Results indicated a significant relationship between TTPD and the total AUC (parent+metabolite). The analysis of response rates indicated that the probability of response was a function of exposure (total AUC of parent+metabolite).
- Limitations: The applicant combined the data from the GIST and MRCC (and solid tumor) studies for their analysis. Their models did include tumor type as a covariate, but only as a scaling factor, which did not allow examination of differences between tumor types in sensitivity or directionality of the E-R relationships.

Exposure-Response for Effectiveness – Agency's Analysis

- The Agency's analysis was done separately for each tumor type. Also, the endpoints modeled were time to tumor progression (TTP) and response rates for partial responses, as these were the primary endpoints in the GIST and MRCC patients respectively. Due to

the limited predictability of the covariate models for clearance, individual clearance estimates from the base model for SU011248 and SU012662 were used for calculating the AUC. As a result, only those subjects with PK data were included in the PK-PD analysis.

- GIST:
  - There was a significant relationship between TTP and exposure (total AUC of parent+metabolite) as indicated by Cox proportional hazards analysis.
  - A significant relationship was also seen for partial response rates and exposure (total AUC of parent+metabolite) in these patients. As expected, increased AUC was associated with longer time to tumor progression.

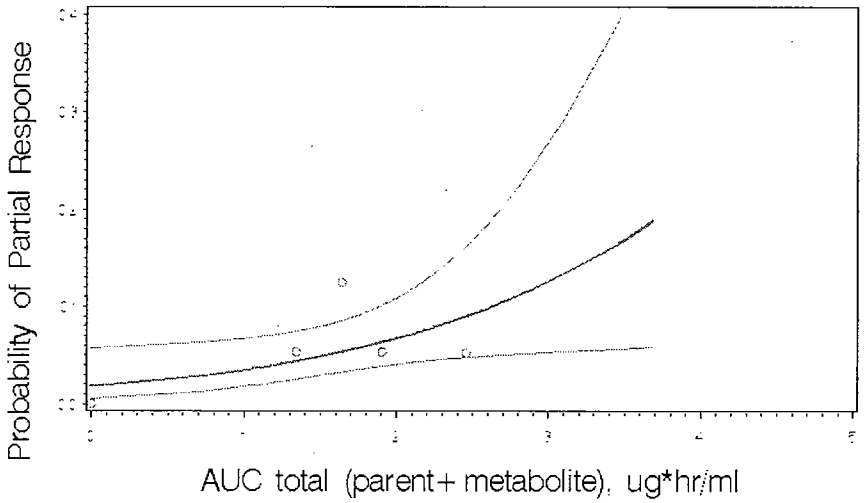


Figure PM1: Probability of partial response vs. total AUC (sunitinib+SU012662) in GIST patients.

  - Females showed a longer time to progression compared to males across studies. Cox proportional hazards analysis indicated a significant gender effect on the steepness of the exposure-TTP relationship.

- MRCC:
  - There was no significant relationship between TTP and exposure in the MRCC patients.
  - There was no significant relationship between partial response rates and exposure in these patients (figure below needs legend).

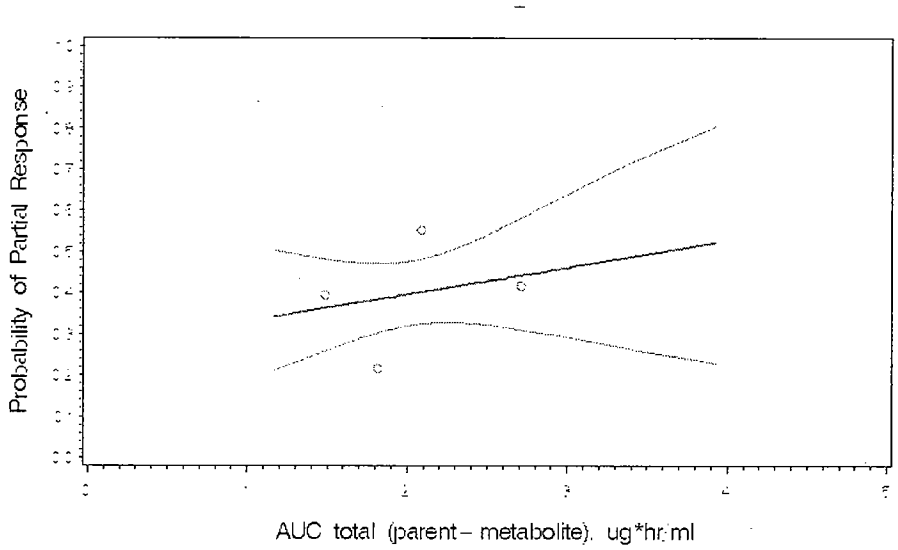


Figure PM2: Probability of partial response vs. total AUC (sunitinib+SU012662) in MRCC patients.

- Additional analyses examined the influence of baseline tumor size on response as well as the effect of exposure on changes in tumor size. These analyses also showed that while increased exposure was associated with larger changes in tumor size for the GIST patients, no relationship was apparent in the MRCC patients.

Exposure-Response for Toxicity:

- The toxicity measures evaluated were those deemed to be probably or definitely related to sunitinib, and the applicant's analysis consisted of exploratory correlations between the toxicity measures and exposure measures. In case of significant correlations, the applicant developed E-R models to better characterize the relationships. PK-PD models were developed for fatigue (using repeated measures logistic regression), diastolic blood pressure (using linear and non-linear regression) and absolute neutrophil counts (using linear and non-linear regression).
- The Agency's analysis included logistic regression to relate the observed frequency of severe grade 3/4 adverse events with exposure in GIST, MRCC and solid tumor patients. Significant relationships were obtained for the incidence of severe fatigue, neutropenia, thrombocytopenia, anemia, vomiting, hypertension and left ventricular ejection fraction dysfunction (see figure below). Exposure-response models were explored for 3 AEs that were quantified as continuous variables: diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF) and absolute neutrophil counts (ANC), as well as for fatigue incidence and severity, quantified as an ordinal variable. These analyses also showed significant relationships for diastolic blood pressure and for fatigue.

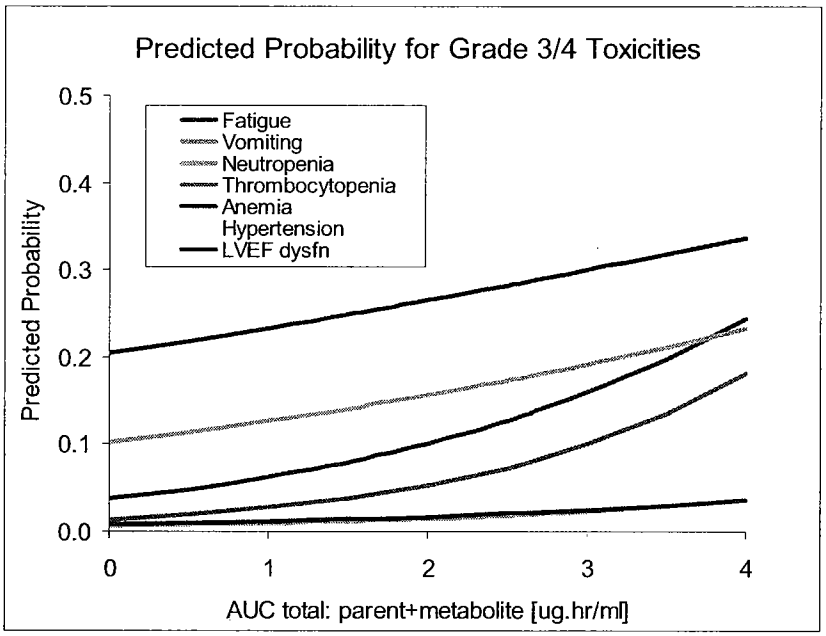


Figure PM3: Predicted probability of severe grade 3/4 toxicities vs. total AUC (sunitinib+SU012662) in GIST and MRCC patients.

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Data:

Data was available for 639 patients: 69 with solid tumors (study 002: 28 and study 005: 41), 402 with GIST (study 013: 97 and study 1004: 304), and 169 with MRCC (study 014: 63 and study 1006: 106). Table PM1 provides a summary of the 6 studies included in the PK-PD analysis

Table PM1: Summary of 6 clinical studies included in PK-PD analysis.

Protocol	Design	Treatment Duration	# Patients Enrolled	Doses	PK Sampling	PD Evaluation	Formulation
248-ONC-0511-002 (Study 002)	dose escalating study in patients with advanced solid tumors	6 week cycles on Schedule 4/2 (4 weeks on drug followed by 2 weeks rest period)	28	25 - 150 mg QD or QOD with dose escalation	full PK profiles taken on day 1 and day 28. at 1,2,3.5,4.5,6.5, 7,8,10,12,14,and 16 hours after dosing; trough level on day 2 and 29 and twice weekly during the first cycle.	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies and clinical assessments weekly. Electrocardiographic assessment, hematology and blood chemistry performed pre-study and twice weekly	Free-base and L-malate salt capsule
RTKC-0511-005 (Study005)	dose escalating study in patients with solid cancer cancer	6 week cycles on Schedule 4/2 or 4 week cycles on Schedule 2/2 (weeks on/off)	42	25-75 mg QD or QOD with dose escalation	full PK profiles taken on day 1 and day 28 at 1,2,3.5,4.5,6.5,7, 8,10,12, 20, 24, and 48 hours after dosing; trough level twice weekly during the first cycle	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies, and clinical assessments weekly. Electrocardiographic assessment, hematology and blood chemistry performed pre-study and weekly	Free-base and L-malate salt capsule
RTKC-0511-013 (Study 013)	open-label, dose-escalating study in GIST patients	6 week cycles on 4/2, 4 week cycles on 2/2, or 3 week cycles on 2/1 (weeks on/off)	97	25 -75 mg QD with dose escalation.	1,4,6,8,10,12,24, and 48 hours post-dose from 18 patients. Trough levels were taken from all patients on days 1,14, and 28	antitumor efficacy based on objective tumor assessments made according to the RECIST system. Laboratory studies, and clinical assessments at day 14 and 28 of cycle 1, day 28 of each additional cycle	L-malate salt capsule
A6181004 (Study 1004)	dual-arm, double-blind, placebo-controlled, multicenter, clinical trial with 2:1 randomization in GIST patients	6 week cycles on Schedule 4/2	304 (total n=357)	50 mg QD, with dose reduction to 37.5 and 25 mg if needed. Dose range: 25-50 mg QD	Trough sampling at day 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 day 14 and 28 of cycle 1, day 28 of each additional cycle	L-malate salt capsule
RTKC-0511-014 (Study 014)	open-label, single-arm, multicenter, clinical trial evaluating the efficacy and safety as single-agent, second-line therapy in RCC patients	6 week cycles on Schedule 4/2	63	50 mg QD with dose reduction if needed. Dose range: 25-62.5 mg QD	Trough sampling at day 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 day 14 and 28 of cycle 1, day 28 of each additional cycle	SU011248 L-malate salt capsule

A6181006 (Study 1006)	open-label, single-arm, multicenter, trial evaluating the efficacy and safety as a single-agent in RCC patients	6 week cycles on Schedule 4/2	106*	50 mg QD. Dose range: 25-62.5 mg QD	Trough sampling at day 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 day 14 and 28 of cycle 1, day 28 of each additional cycle	L-malate salt capsule

Exposure measures were calculated based on individual patient estimates of the parameters of a two-compartment population pharmacokinetic model for SU011248 and a separate two-compartment model for its primary metabolite SU012662. The applicant had computed several measures of exposure including: steady-state AUC, trough concentrations (C_{trough}), a cumulative AUC over time, and a "windowed" AUC which includes a cumulative AUC over the 28-day interval preceding the assessment. Different measures of exposure were used in E-R analysis of different PD measures.

Our analysis used the 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 SU011248 and SU012662 were used for calculating the AUC. As a result, only those subjects with PK data were included in the PK-PD analysis.
This was similar to the method used by the sponsor, except that we used the posthoc estimates from the final model obtained by fitting the data across all 13 studies with PK data included in the submission, while the applicant used the final model parameters obtained by fitting the data only across the 6 studies included in the PKPD analysis. Most of the data in these studies are trough levels, particularly in the MRCC patients, and there would be a concern about how well the model was able to fit these data. Also, our analysis used the average dose received by the subject across cycles of exposure rather than the nominal dose to provide a more realistic estimate of exposure given the dose reductions which were seen in 11-12% of GIST patients and 22-40% of MRCC patients.

The response measures were divided into 2 categories: effectiveness measures and toxicity measures.

The effectiveness measures were:

- objective response rates (ORR)
- time to tumor progression (TTP)
- overall survival (OS)
- time to progression or death (TTPD) or progression-free survival (PFS)
- duration of response (DR)

The applicant's E-R analysis focused on TTPD and objective response rates. TTPD was modeled using parametric survival analysis. Objective response rates were modeled using repeated measures logistic regression.

Our analysis focused on TTP and ORR as these were the primary endpoints for the GIST and MRCC trials, respectively.

For TTP, our analysis included an exploratory non-parametric Kaplan-Meier analysis and a parametric survival analysis. We also analyzed the overall survival data in the same way. For ORR, our analysis was a logistic regression of the partial response rates.

Another major difference was that the applicant combined the data from the GIST and MRCC (and solid tumor) studies for their analysis. Their models did include tumor type as a covariate, however it was usually included simply as a scaling factor, and could not account for differences in sensitivity or directionality in the E-R relationships between GIST and MRCC patients.

The toxicity measures evaluated were those deemed by clinical investigators to be probably or definitely related to sunitinib:

- Fatigue, graded according to NCI Common Toxicity Criteria (NCI CTC) v. 3.0
- Nausea, graded according to NCI CTC v. 3.0
- Vomiting, graded according to NCI CTC v. 3.0
- Hypertension, measured by absolute diastolic blood pressure and its change from baseline
- Left-Ventricular Ejection Fraction, estimated from ECHO or MUGA scans and measured by absolute value and change from baseline
- Neutropenia, assessed by absolute neutrophil count (ANC)
- Thrombocytopenia, assessed by platelet count
- Anemia, assessed by red blood cell count
- Pancreatic Function, assessed by measurement of serum lipase and amylase activity

The applicant's analysis consisted of exploratory correlations between the toxicity measures and exposure measures. In case of significant correlations, the applicant developed E-R models to better characterize the relationships. PK-PD models were developed for:

- fatigue (using repeated measures logistic regression)
- diastolic blood pressure (using linear and non-linear regression)
- absolute neutrophil counts (using linear and non-linear regression)

Our analysis mainly involved logistic regression analysis to relate the observed frequency of each of the above AEs with exposure (AUC) in GIST, MRCC and solid tumor patients. Additionally, PK-PD models were examined for 3 AEs that were quantified as continuous variables: diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF) and absolute neutrophil counts (ANC), as well as for fatigue incidence and severity, quantified as an ordinal variable.

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.

Review:

This review is organized under the following sections. Under each section, the applicant's analysis will be summarized and followed by our analysis and interpretation.

- E-R for effectiveness of sunitinib
  - Applicant's analysis: TTPD and ORR across tumor types
  - Agency's analysis:
    - GIST: time to tumor progression (primary endpoint), and response rates.
    - MRCC: response rates (primary endpoint), and time to tumor progression.
    - Effect of covariates (including sex and baseline tumor size) on E-R relationships for effectiveness.
    - E-R for changes in tumor size during treatment.

- E-R for toxicity of sunitinib in GIST, MRCC and solid tumor patients.
  - Applicant's analysis: fatigue, diastolic blood pressure, ANC
  - Agency's analysis :
    - logistic regression
    - modeling of fatigue, diastolic blood pressure, LVEF and ANC.
    - Effect of covariates on E-R relationships for toxicity.

- Population Pharmacokinetic Analysis

I. E-R FOR EFFECTIVENESS OF SUNITINIB

Applicant's analysis: TTPD and ORR across tumor types

The applicant's E-R analysis focused on TTPD and objective response rates. TTPD was modeled using parametric survival analysis. Objective response rates were modeled using repeated measures logistic regression. In both cases, data were modeled across the GIST, MRCC and solid tumor patients, and tumor type was evaluated as a covariate in the analyses.

1) Parametric survival analysis: A Weibull time-to-event model was fit to the time to progression or death (which was not the primary endpoint). The "rate constant" of the Weibull function (lambda) was modeled as a function of exposure (AUC) and tumor type was used as a covariate to determine if different tumor types had different "rate constants" for the survival function:

$$S(t)=\exp(-\text{lambda}\cdot t)^{\text{gamma}}$$

$$\text{lambda} = \ln 2/((Eo+Slp\cdot \ln AUC)\cdot K_{tumor})$$

where Eo is the baseline, Slp is the slope of the lambda-AUC relationship, and K_{tumor} is an estimated factor that varied with tumor type.

Several models, including linear, log-linear (the final model, shown above) and Emax models, were used to model the effect of exposure. Results showed that the time to progression was a function of exposure, and tumor type was a significant covariate. However, as the equation above indicates, the above model presumes the same basic model structure for the GIST and MRCC patients, and does not allow the directionality of the relationship (TTP increasing with

exposure for one tumor type and decreasing with exposure for another tumor type) to vary by tumor type).

2) Response Rates: For the analysis of response rates, the RECIST response was coded as a multinomial variable (m=0 for complete response, =1 for partial response, =2 for stable disease and =3 for progressed disease), and modeled as a function of exposure using repeated measures logistic regression. Both linear and Emax models were evaluated. The model equation for logit (log odds) of the probability of response ≥ m was:

$$\text{logit } P(Y \geq m \mid Y>0) = B_m + Pmax*(1-\exp(-K*t) + f(\text{exposure})$$

where B_m: intercept, i.e., response rate for severity=m at time 0 with no drug.
Pmax: maximum placebo response
K: rate constant for placebo response
f(exposure): a function of exposure.

Linear (SLP2*AUC) and Emax (Emax*AUC/(EC50+AUC)) models were evaluated. The Emax exposure expression was selected as providing the best fit. However, the EC50 estimate obtained was very small and was poorly estimated, suggesting that exposures were well over EC50 at the studied doses. Also, tumor type was not a significant covariate and was not included in the final model.

In summary, the applicant's analysis did not reveal any robust quantitative relationships between exposure and measures of effectiveness. Possible reasons for this included the small range of doses and exposures used in the studies, and a large variability in response measures, which could be partly attributed to the combining of data across tumor types. This could be particularly relevant due to the differences in responses by tumor type seen in the Agency's analysis (as described below)

Agency's analysis:

A. **GIST: time to tumor progression (primary endpoint), and response rates.**
B. **MRCC: response rates (primary endpoint), and time to tumor progression.**
C. **Effect of baseline tumor size on E-R relationships for effectiveness.**
D. **E-R for changes in tumor size during treatment.**

A. E-R for effectiveness in GIST: time to tumor progression (TTP) and response rates

Question: What is the exposure-response relationship for the primary effectiveness endpoint, time to tumor progression (TTP), for sunitinib in patients with GIST?

Kaplan-Meier curves:
There were 401 GIST patients in study 13 and 1004. The investigator-confirmed TTP data for these patients was used to generate Kaplan-Meier curves, by treatment (sunitinib 50 mg vs. placebo). To explore the potential for a relationship between TTP and exposure, the data were divided into quartiles based on the total AUC (AUCtot, parent+metabolite), and Kaplan Meier curves were generated, by AUCtot quartiles.

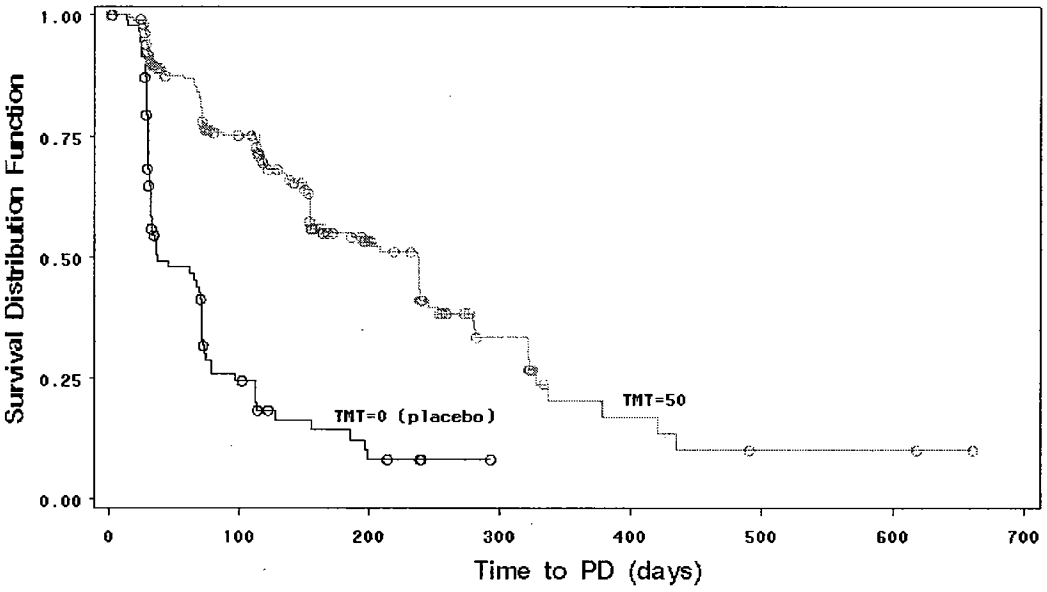

Figure PM4: Time to tumor progression (TTP) for GIST patients, by treatment (TMT=0 for placebo, TMT=50 for sunitinib).

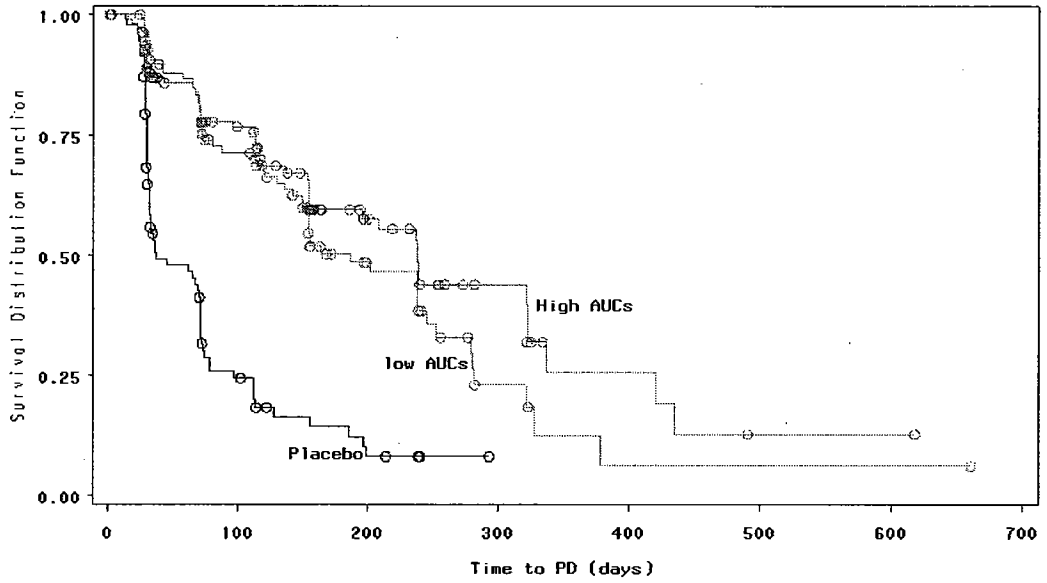

Figure PM5: Time to tumor progression (TTP) for GIST patients, by AUCtot median split. Low AUCs < median (1.77 ug.hr/ml) and High AUCs above mediam.

As figure 1 indicates, there appears to be a treatment-related difference in TTP for the GIST patients. Figure 2 suggests an exposure-related increase in TTP, with the higher AUCs showing higher TTP compared to the lower AUCtot quartiles (bins 2 and 3).

Parametric Survival Function:
A parametric Weibull distribution model, similar to that used by the applicant, was used to characterize the TTP data, and to examine the effect of exposure on the TTP. The model equation for the survival function (S(t)) was as follows:

$$S(t) = \exp((-\text{lambda}\bullet * t)^{\text{gamma}})$$

where gamma is a "shape" parameter characterizing the Weibull distribution. If gamma = 1, the Weibull distribution reduces to an exponential distribution.
lambda is the "scale" parameter characterizing the rate constant for the distribution as a function of time.

To examine the effect of exposure, lambda was modeled as a function of exposure using linear and Emax models, as shown below. The sponsor has used log-linear models as well, as their data did not include any patients on placebo.

Linear Model: lambda = ln2/(Baseline+Slope•Exposure)
Emax Model : lambda = ln2/(Baseline+(Emax•Exposure)/(EC50+Exposure))

Exposure measures used included ISTRT (a binomial variable with value of 0 for placebo and 1 for sunitinib treatment) and AUCtot (AUC for parent+metabolite).

The effect of sex as a covariate was modeled by multiplying the denominator in the above equations by (1+θsex*SEX).

Results: The following table shows the summary of the model fitting.

Table PM2: Results of parametric survival model fitting to data from GIST studies.

No.	Model	OBJ	B1	gamma	Slope	Emax	EC50	TSEX	ETA
I	Linear-ISTRT	2148.699	60.4	2.07	133	-	-	-	74%
II	Linear-ISTRT +SEX	**2141.089**	53.5	2.09	116	-	-	0.433	73%
III	Linear - AUCtot	2156.461	61.8	1.94	75.1	-	-	-	73%
IV	Linear-AUCtot +SEX	2151.276	56.2	1.94	66.8	-	-	0.355	72%
V	Emax-AUCtot	2148.699	60.5	2.07	-	133	1.3E-7	-	74%
VI	Emax-AUCtot +SEX	2141.089	53.5	2.09	-	116	1.3E-7	0.433	73%

Model II, which included TRT as a binomial variable, in a linear function was determined to be the best fitting model. Inclusion of sex as a covariate decreased the objective function significantly (ΔOBJ=7.6), indicating that sex was a significant covariate in the survival model for GIST.

The following figure shows the predicted survival function for the GIST patients. The predicted curves are superimposed on the Kaplan-Merier curves for TTP for the placebo (istrt=0) and sunitinib (istrt=1) patients, by gender. As the figure shows, females had a slower time to progression compared to males. This is consistent with the non-parametric and semi-parametric analysis discussed above.

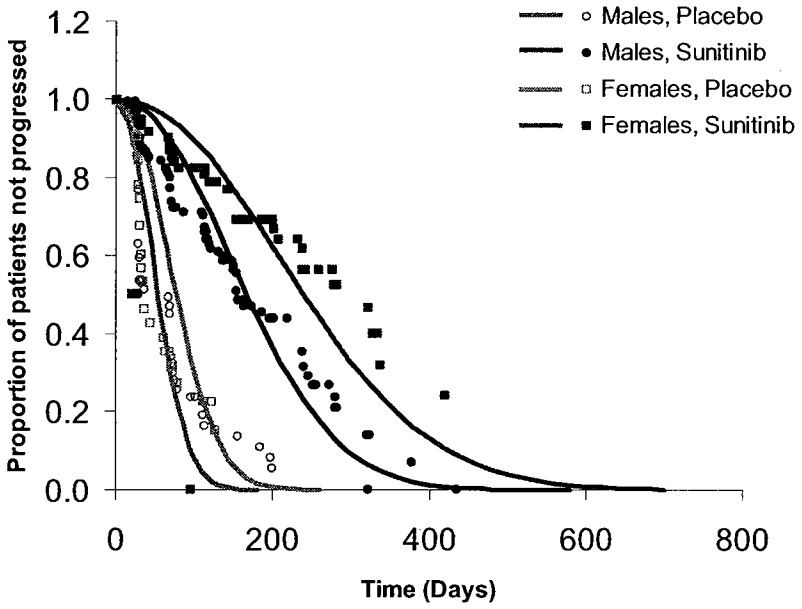

Figure PM6: Estimated survival function (proportion of patients not progressing) as a function of time. Four groups are plotted: placebo and sunitinib for males and placebo and sunitinib for females. Solid lines represent curves based on best-fitting model.

Question: What is the exposure-response relationship for the secondary endpoints: overall survival, and objective response rates, for sunitinib in GIST patients?

Overall Survival

Kaplan-Meier curves:
Kaplan-Meier curves for overall survival (OS) were generated by treatment (placebo vs. sunitinib). To explore the potential for a relationship between OS and exposure, the data were divided into quartiles based on AUCtot, as done for TTP, and Kaplan-Meier curves were generated, by AUCtot quartiles.

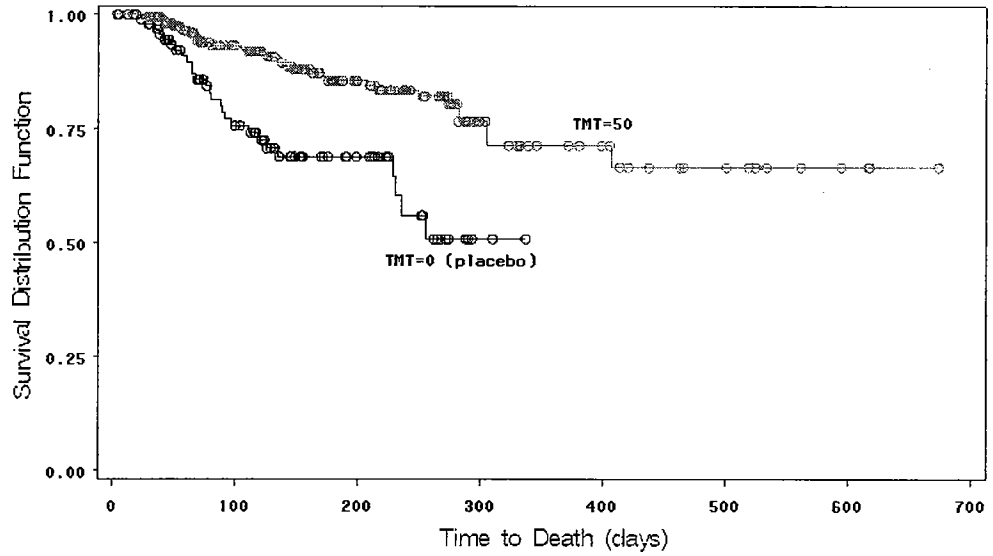

Figure PM7: Overall survival (OS) for GIST patients, by treatment (TMT=0 for placebo, TMT=50 for sunitinib).

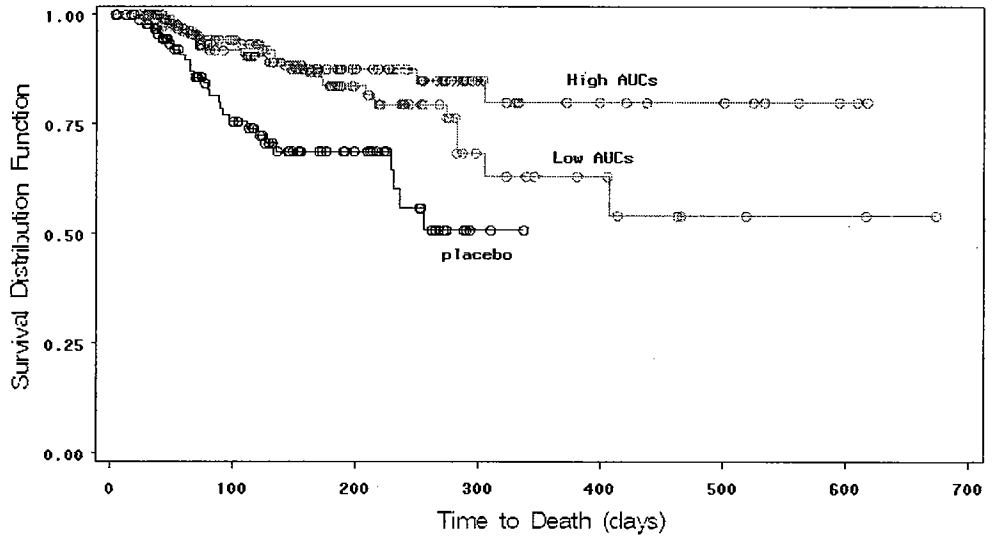

Figure PM8: Overall survival (OS) for GIST patients, by AUCtot median split. Low AUCs (AUC < median), High AUC (AUC>median).

As figure PM7 indicates, patients on sunitinib showed a higher survival rate compared to placebo. When the Kaplan-Meier curves were plotted by AUCtot median split, there was some indication of exposure-related differences in overall survival.

Parametric survival analysis was not performed for overall survival or TTPD, as the data was not considered to be mature (<50% events had occurred) at the time of analysis.

c) Objective Response Rates

Objective response to treatment was classified using RESICT criteria as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Disease Progression (PD).
The following table shows the best objective response rates, by treatment, for studies 13 and 1004.

Table PM3: Best objective response rates for GIST studies, by treatment.

(Investigator-assessed) Response [n (%)]	Study 1004		Study 13
	Sunitinib 50 mg QD (N=207)	Placebo (N=105)	Sunitinib 50 mg QD (N=55)
Complete Response	0 (0)	0 (0)	0 (0)
Partial Response	15 (7.2%)	0 (0)	5 (9.1%)
Stable Disease	94 (45.4%)	26 (24.8%)	41 (74.5%)
Disease Progression	26 (12.6%)	42 (40.0%)	5 (9.1%)
Not evaluable	47 (22.7%)	23 (21.9%)	3 (5.5%)
Missing	25 (12.1%)	14 (13.3%)	1 (1.8%)

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 GIST patients. The effect of sex and ECOG score (only ECOG=1 was evaluated since there were only ZZ patients with ECOG score=2) were also examined.

The following table shows the results of the logistic regression analysis for proportion of patients with partial responses (ISPR, =1 for responders, =0 for non-responders).

Table PM4: Results of logistic regression analysis of proportion of partial responses in GIST patients.

	Independent variables	AIC	Estimate	SE	p-value	Odds Ratio
I	Intercept	129.6				
II	Intercept	126.4	-4.02	0.62	0.0001	
	AUCtot		0.69	0.32	0.0311	1.99 (1.07-3.75)
III	Intercept	128.9	-3.98	0.66	0.0001	
	AUCtot		0.67	0.32	0.0387	1.95 (1.04-3.67)
	SEX		0.49	0.53	0.3477	
	ECOG1		-0.44	0.53	0.4072	

There was a significant relationship between frequency of partial responses and AUCtot. The odds ratio of 1.99 indicates that there was a 2-fold increase in frequency of partial responses per unit increase in AUCtot. Sex and ECOG score were not significant covariates in this relationship.

The following graph shows the predicted probability of partial responses as a function of AUCtot.

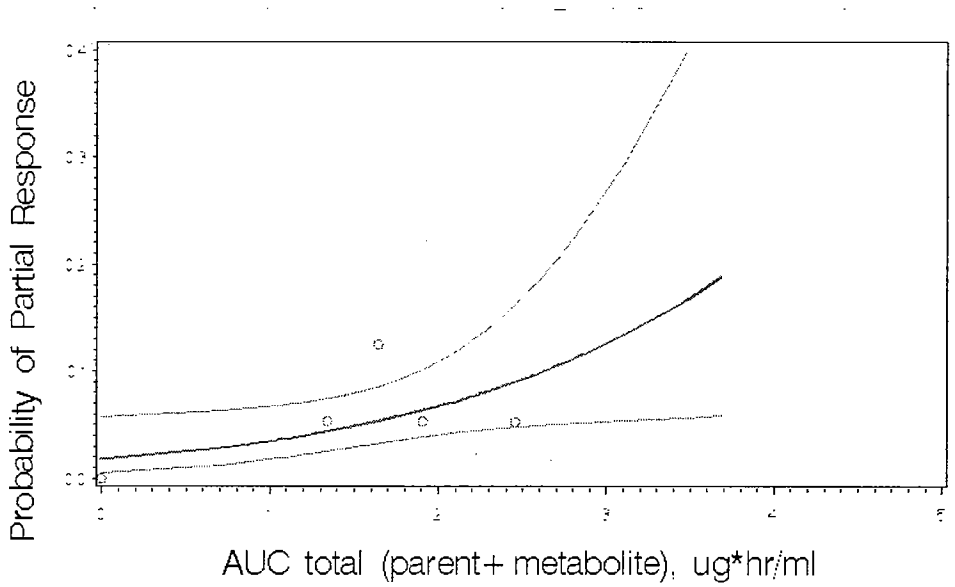

Figure PM9: Probability of partial responses (based on RECIST criteria) vs. AUC total (parent+metabolite) for patients with GIST.

In summary, there was an exposure-related increase in response rates for partial responses in GIST patients. Neither sex nor ECOG scores had any additional effect on this relationship in these patients.

B. E-R for effectiveness for MRCC: response rates and time to tumor progression (TTP)

Question: What is the exposure-response relationship for the primary effectiveness endpoint, objective response rate, for sunitinib in patients with MRCC?

Data for MRCC patients were obtained from 2 studies, #14 and #1006. Both were single arm studies of 50 mg sunitinib. Response rates were assessed using RECIST criteria, which are based on measurements of tumor size. The following table shows the response rates for the MRCC studies:

Table PM5: Best objective response rates for MRCC studies, by treatment.

	Study 1006	Study 14
(Investigator-assessed) Response [n (%)]	Sunitinib 50 mg QD N=106	Sunitinib 50 mg QD N=63
Complete Response (CR)	1 (0.9%)	0 (0%)
Partial Response (PR)	37 (34.9%)	23 (36.5%)
Stable Disease (SD)	44 (41.5%)	25 (39.7%)
Disease Progression (PD)	17 (16.0%)	7 (11.1%)
Not evaluable	7 (6.6%)	5 (7.9%)
Missing	0 (0%)	3 (4.8%)

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 effect of sex and ECOG score (only ECOG=1 was evaluated since there were only 10 patients with ECOG score=2) were also examined.

This analysis differs from that done by the sponsor, in which the response rate was modeled using a conditional logistic regression model (response rate=0 for CR, =1 for PR, =2 for SD, =3 for PD).

The following table shows the results of the logistic regression analysis for proportion of patients with partial responses (ISPR, =1 for responders, =0 for non-responders).

Table PM6: Results of logistic regression analysis of proportion of partial responses in MRCC patients.

	Independent variables	AIC	Estimate	SE	p-value	Odds Ratio
I	Intercept	202.1				
II	Intercept	203.4	-0.97	0.71	0.1756	
	AUCtot		0.27	0.34	0.4311	
III	Intercept	200.0	-1.0	0.74	0.1795	
	AUCtot		0.55	0.38	0.1471	
	SEX		-0.56	0.39	0.1575	
	ECOG1		-0.81	0.35	0.0230	0.45 (0.23 – 0.90)

The following graph shows the predicted probability of partial responses as a function of AUC.

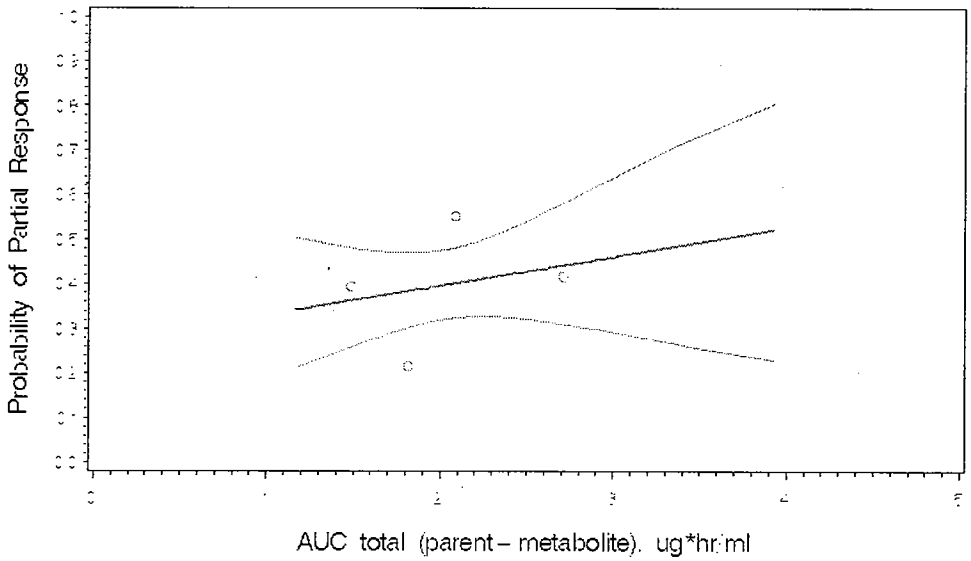

Figure PM10: Probability of partial responses (based on RECIST criteria) vs. AUC total (parent+metabolite) for patients with MRCC.

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

Question: What is the exposure-response relationship for secondary endpoints, TTP, and overall survival, for sunitinib in patients with MRCC?

a) Time To Tumor Progression (TTP)

Kaplan-Meier curves:
There were 169 MRCC patients in study 14 and 1006. The TTP data for these patients was used to generate Kaplan-Meier curves. To explore the potential for a relationship between TTP and exposure, the data were divided into quartiles based on the total AUC (AUCtot, parent+metabolite), and Kaplan Meier curves were generated, by AUCtot quartiles.

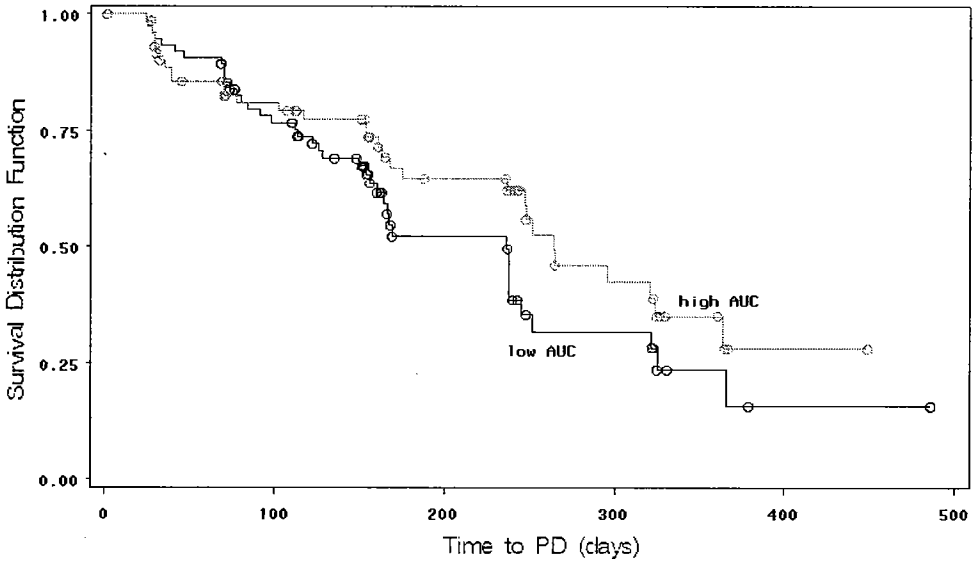

Figure PM11. Time to tumor progression (TTP) for MRCC patients, by AUCtot median split. Low AUC: AUC<median (1.9 ng/ml), High AUC: AUC> median.

As figure 10 shows, the high AUC group appears to show a somewhat longer time to progression compared to the low AUC group.

Parametric Survival Function:
A parametric Weibull distribution model, identical to the model described above for TTP in GIST patients, was used to characterize the TTP data in MRCC patients, and to examine the effect of exposure on the TTP.

Results: The following table shows the summary of the model fitting.

Table PM7: Results of parametric survival function model fitting to data from MRCC studies.

No.	Model	OBJ	B1	gamma	Slope	Emax	EC50	TSEX	ETA
I	Linear model-ISTRT	1083.982	224	1.76	3.35	-	-	-	83%
II	Linear - AUCtot	**1075.010**	90.1	1.83	78.1	-	-	-	79%
III	Emax-AUCtot	1072.555	81.2	1.9		163	2.2E-6	-	79%
IV	Linear-AUCtot-Sex	1073.891	98.9	1.87	83.3	-	-	-0.192	79%

Model II, which included AUCtot in a linear function was determined to be the best fitting model. Using an Emax model for the E-R relationship showed a reduction in OBJ that was less than the criteria of 3.84 for inclusion at the p=0.05 level. Inclusion of SEX as a covariate in the linear model also did not reduce the OBJ significantly.

The following figure shows the estimated TTP for 2 groups of patients, classified based on their AUCs into a low AUC and high AUC group.

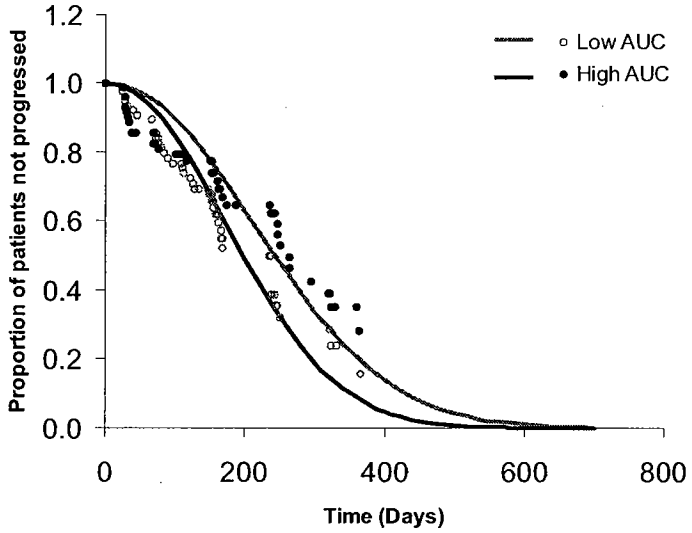

Figure PM12: Estimated survival function (proportion of patients not progressing) as a function of time to tumor progression in MRCC patients, for low AUC (< median) and high AUC (> median). Solid lines represent curve from best-fitting model.

b) Overall Survival

Kaplan-Meier curves:

Kaplan Meier curves were generated for overall survival or OS for the MRCC patients in study 14 and 1006. To explore the potential for a relationship between OS and exposure, the data were

divided into quartiles based on the total AUC (AUCtot, parent+metabolite), and Kaplan Meier curves were generated, by AUCtot quartiles.

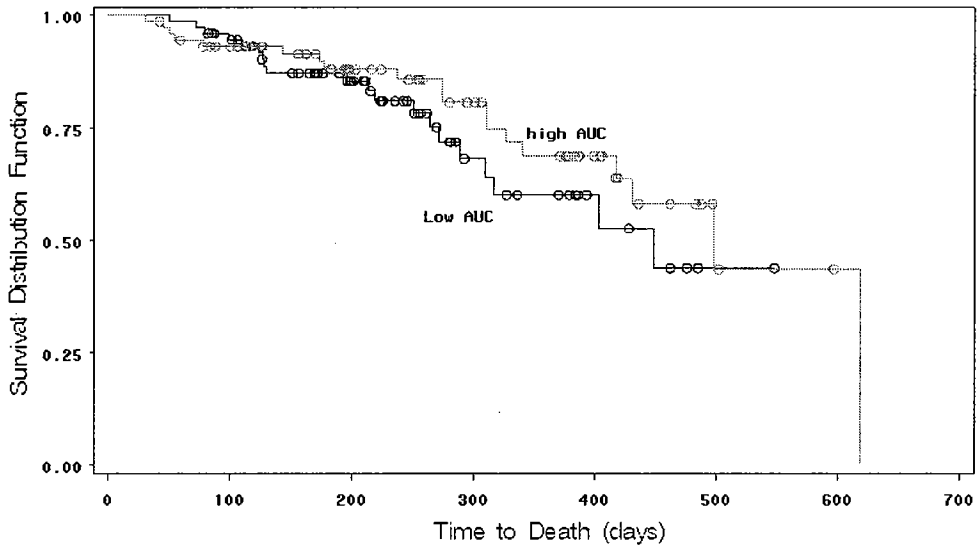

Figure PM13: Overall survival (OS) for MRCC patients, by AUCtot median split. Low AUC: AUC < median, High AUC: AUC> median.

As figure 13 shows, the high AUC group shows a slightly higher overall survival compared to the low AUC group.

Parametric survival analysis was not performed for overall survival as the data was not considered to be mature (<50% events had occurred) at the time of analysis.

Question: What is the role of sex in the E-R relationship for effectiveness measures in GIST patients?

1. K-M curves for TTP show slower progression for females (red in figure below) than for males (black in figure below) receiving 50 mg sunitinib. The same trend is not seen in placebo patients. [note: X-axis scales are different]

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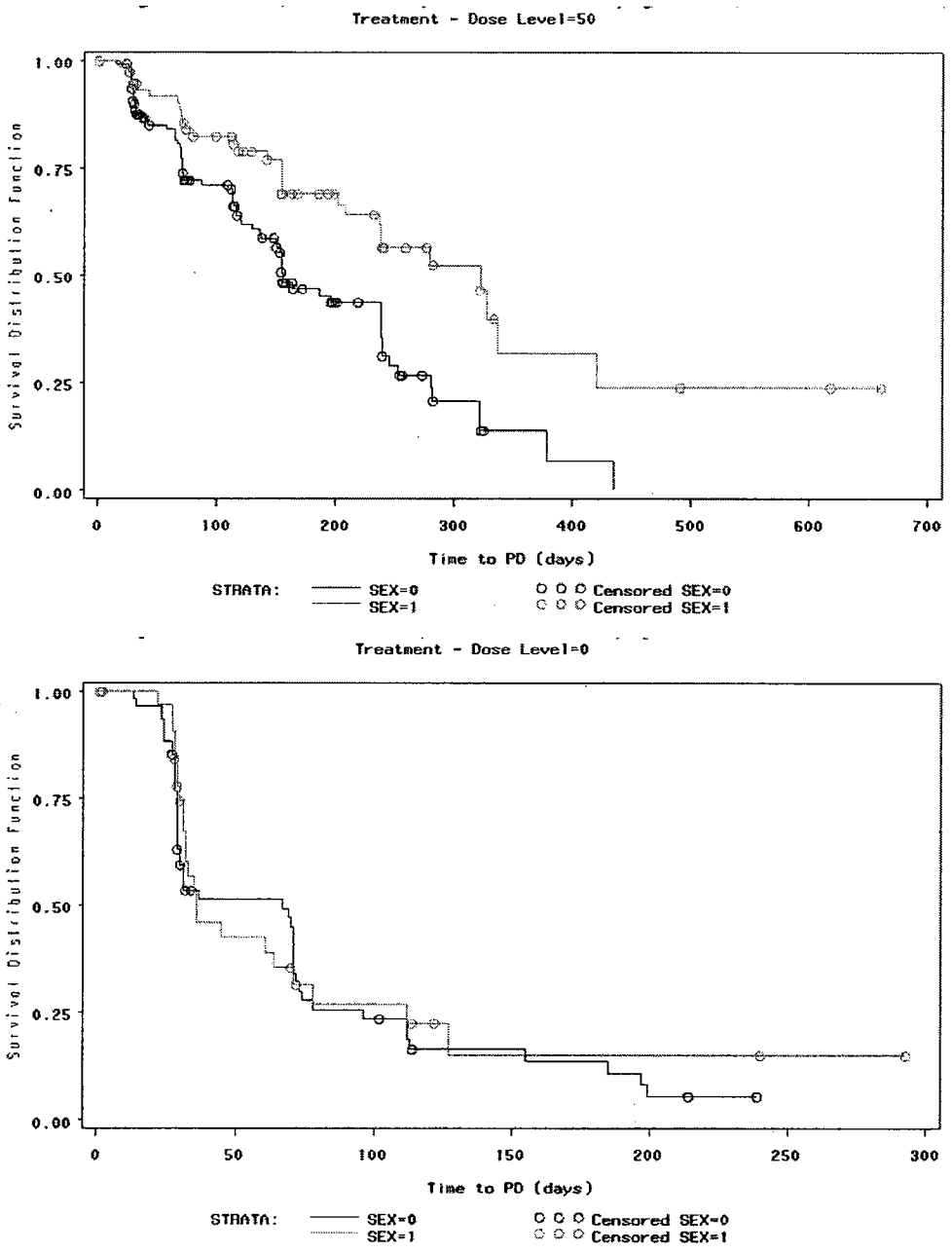

Figure PM14: Kaplan-Meier curves for time to tumor progression, by gender, in GIST patients following 50 mg sunitinib (upper panel) or placebo (lower panel). Sex=0 (black) refers to males, Sex=1 (red) refers to females.

2. Rates of progression (RR for Progression based on RECIST) also showed a trend toward lower values for females compared to males, in the active treatment group (quartiles).

Table PM8: Frequency of rate of progression (based on RECIST) for males and females.

GROUP	**Males Counts (%)**	**Females Counts (%)**
Placebo	26/63 (41.3%)	15/38 (39.5%)
Sunitinib	18/145 (12.4%)	6/80 (7.5%)
GROUP	**Males**	**Females**
Placebo	26/63 (41.3%)	15/38 (39.5%)
AUCtot Quartile 1	3/44 (6.8%)	0/12 (0.0%)
AUCtot Quartile 2	6/37 (16.2%)	1/19 (5.2%)
AUCtot Quartile 3	4/37 (10.8%)	1/19 (5.2%)
AUCtot Quartile 4	5/27 (18.5%)	4/30 (13.3%)

Could this apparent difference be due to gender differences in PK or gender differences in PD (sensitivity) or both?

Gender differences in PK:

Analysis indicates an apparent gender difference in sunitinib and active metabolite clearances.
a) Non-compartmental PK parameters from two phase 2 studies (002 and 005) in which doses of 25 to 100 mg of sunitinib were administered to male and female solid tumor patients were examined for gender differences. The following table shows the mean apparent clearance of sunitinib and dose-normalized AUC of parent and metabolite in males and females from these studies (clearance of metabolite was not determined).

	Males (n=37) Mean (SD)	Females (n=32) Mean (SD)
CL/F for Sunitnib [L/hr]	66.3 (28.8)	51.0 (29.2)
Dose-normalized AUCinf for Sunitinib [(ng.hr/ml]/mg]	20.9 (17.6)	27.8 (15.5)
Dose-normalized AUCinf for SU012662 [(ng.hr/ml]/mg]	8.3 (21.1)	8.8 (8.7)
Dose-normalized AUCinf of total(Sunitnib+SU012662) [(ng.hr/ml]/mg]	28.7 (30.6)	34.6 (15.6)

There was large variability in AUCs across individuals. Females showed a 33% higher AUC for sunitinib compared to males, and 6% higher AUC for the metabolite compared to males.

b) Population PK models showed a significant effect of gender on the clearance of sunitinib and its active metabolite. Based on the covariate models, typical clearances in male and female GIST patients were estimated and from these, AUCs for the 50 mg dose was calculated.

	AUC(parent)	AUC(metabolite)	AUC(total)
Males	1.46 µg.hr/ml	0.5 µg.hr/ml	1.96 µg.hr/ml
Females	2.25 µg.hr/ml	0.8 µg.hr/ml	3.05 µg.hr/ml

Comparison of the total AUC (parent+metabolite) indicated that females had a 50% higher exposure than males.

The higher exposure in females could partially explain the apparent gender difference in TTP.

Gender differences in PK-PD:

K-M curves for TTP also showed an effect of exposure – patients with high AUCs (above the median) showed a slower TTP than patients with low AUCs (below the median) (see figure 2 above).

Cox proportional hazards analysis of TTP showed a significant negative effect of AUC, i.e., a decrease in risk of progression with increase in AUC. The hazard ratio was 0.5 indicating a 50% decrease in risk of progression for each unit increase in AUC [average AUC for 50 mg dose is ~1.8 ug.hr/ml]

Given this exposure-TTP relationship, we wanted to determine if there was an effect of gender on TTP, after accounting for the effect of exposure.

Results: Cox proportional hazards analysis:

Model	Independent Variable	Coefficient	p-value	Hazard Ratio
I	AUCtotmean	-0.668	<0.0001	0.513
II	AUCtotmean	-0.637	<0.0001	0.529
	Sex	-0.331	0.2137	0.718
	AUCtotmeanXSex	-0.050	0.7864	0.951

Results from Model II indicate that there is no significant main effect of sex or significant interaction between AUC and sex in the relationship with TTP.
As the observed proportion of females and males showing progression was similar in the placebo group (see table on previous page), and appeared to differ under active drug, we wanted to evaluate the effect of sex on the steepness (or slope) of the exposure-TTP relationship. Operationally, this is the same as looking at the AUCxSEX interaction without looking at the main effect of SEX in the regression analysis (Model III).

Model	Independent Variable	Coefficient	p-value	Hazard Ratio
III	AUCtotmean	-0.573	<0.0001	0.564
	AUCtotmeanXSex	-0.229	0.0454	0.795

The above results indicate a significant effect of sex on the exposure-TTP relationship. Due to the significant interaction, the relative risk of progression for males and for females will depend on the AUC, and can be calculated as [exp(b1+b2*sex)]. So, for AUC=1, the relative risk for progression in males can be estimated as 0.56 [exp(-0.573-0.229*0)] and for females as 0.45 [exp(-0.573-0.229*1)]. Similarly, the relative risk of progression can be calculated at the typical AUC (1.75 ug.hr/ml) for the 50 mg sunitinib dose. The relative risk at this AUC is 0.367 for males and 0.246 for females.
The hazard ratio of 0.795 reported in the table above is the ratio of the hazard ratios for females to males when AUC=1, therefore must be interpreted with caution at other values of AUC.

The following figure shows the calculated relative risk of progression as a function of AUC for males and females based on Model III.

These results are less robust when only data from the placebo-controlled study 1004 are included in the analysis. The p value for AUC X SEX interaction is 0.11.

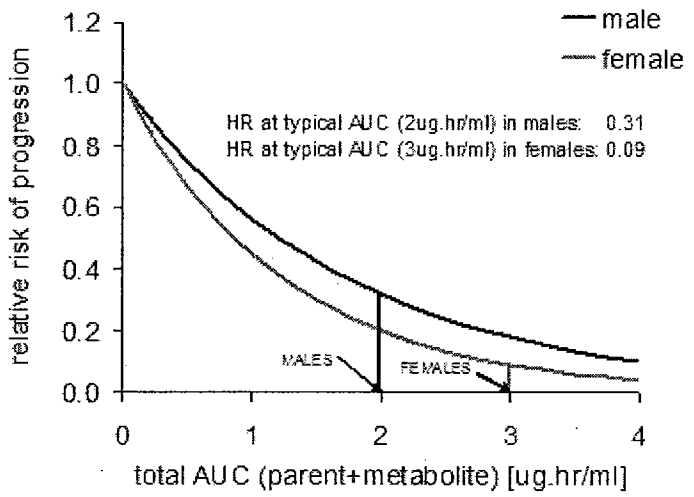

Figure PM15: Relative risk of tumor progression vs. AUC in GIST patients.

In summary, the PK analysis showed that females have a 50% higher exposure (sunitinib + metabolite) compared to males. The preceding analysis showed that females also have a lower time to progression compared to males. Females may be more sensitive to the effects of the drug than males. As these analyses were based on investigator assessments of tumor progression, these results will need to be confirmed using the core lab assessments of tumor progression prior to any recommendations regarding gender and sunitinib dosing.

No gender differences were seen in the MRCC patients, although the data in MRCC patients did not demonstrate a clear E-R relationship either. However, male MRCC patients in general do have a poorer prognosis and so, gender differences should be also examined in this population.

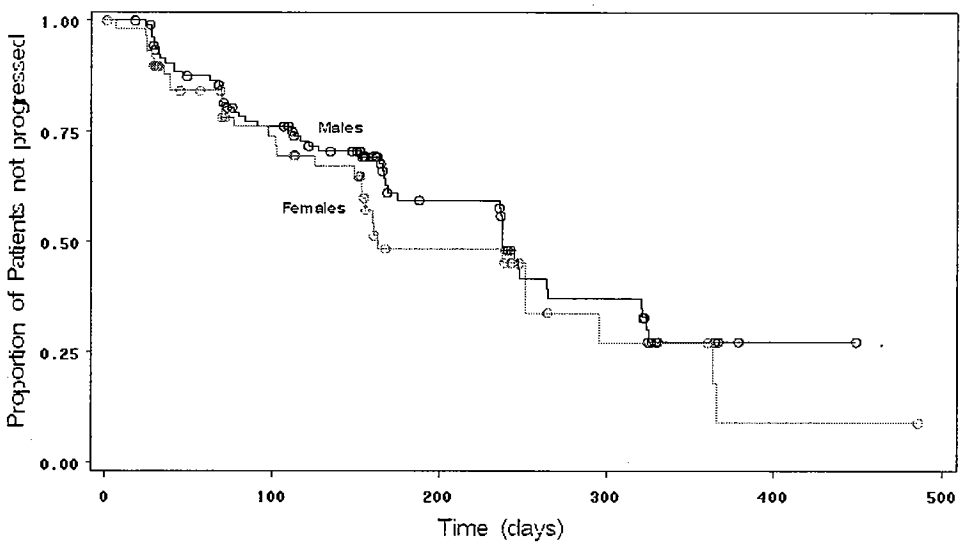

Figure PM16: Kaplan-Meier curves for time to tumor progression, by gender, in MRCC patients following 50 mg sunitinib. Sex=0 (black) refers to males, Sex=1 (red) refers to females.

C. Effect of baseline tumor size on E-R relationships for effectiveness.

GIST

Question: Does the baseline tumor size affect time to tumor progression (TTP) or overall survival (OC) in GIST patients?

To explore the effect of baseline tumor size, the patients were classified into 4 groups, based on quartiles of baseline tumor size. Kaplan-Meier curves for TTP and OS, by baseline tumor size quartiles were plotted.

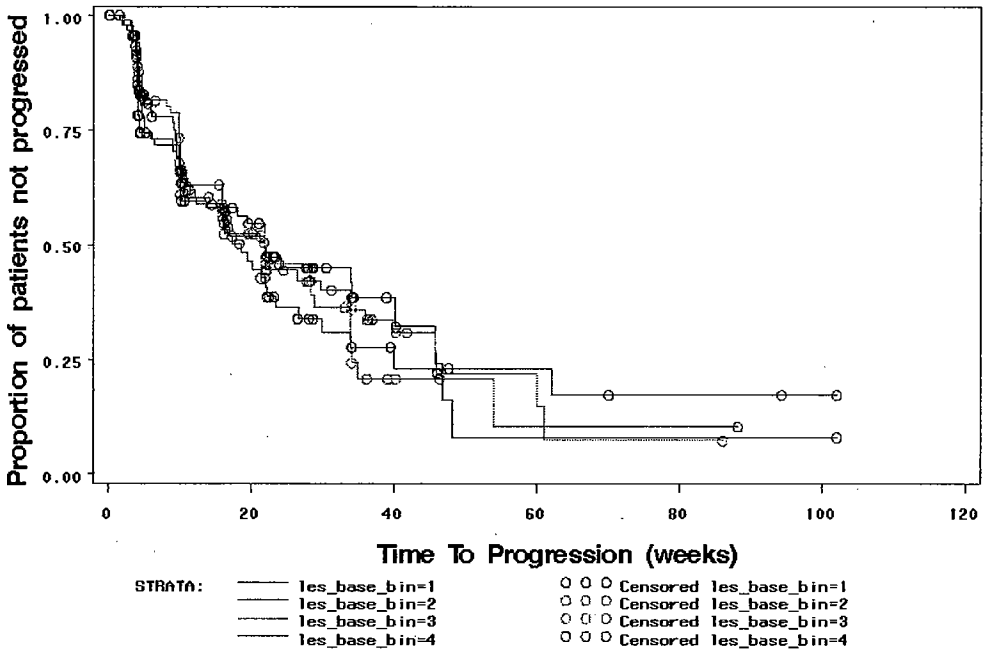

Figure PM17: Time to tumor progression for GIST patients classified into 4 groups based on baseline tumor size quartiles.

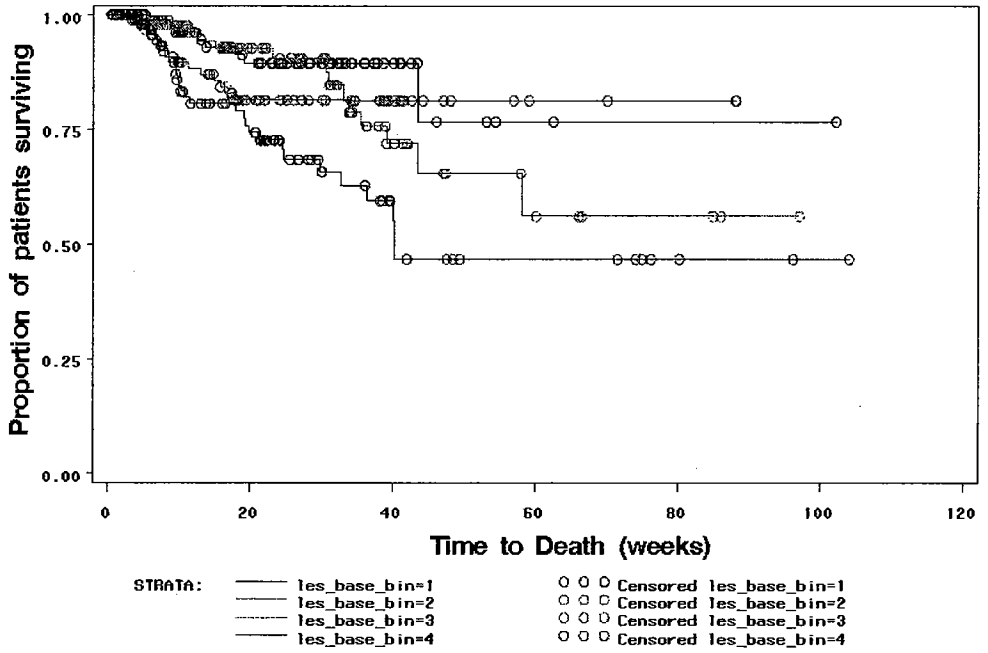

Figure PM18: Time to death for GIST patients classified into 4 groups based on baseline tumor size quartiles.

The above plot for TTP does not indicate any differences among groups classified by baseline tumor size in GIST patients.

GIST	1st Quartile Bin 1	2nd Quartile Bin 2	3rd Quartile Bin 3	4th Quartile Bin 4
Baseline Tumor size [mm]	0 – 131.5	131.5 – 210.75	210.75 – 339	> 339

The plot for OS suggests that patients with higher baseline tumor size (4th quartile, blue) showed shorter OS than patients with lower baseline tumor size (1st quartile, black) in GIST patients. This is somewhat clearer when the baseline tumor sizes were classified based on a median split, as shown below.

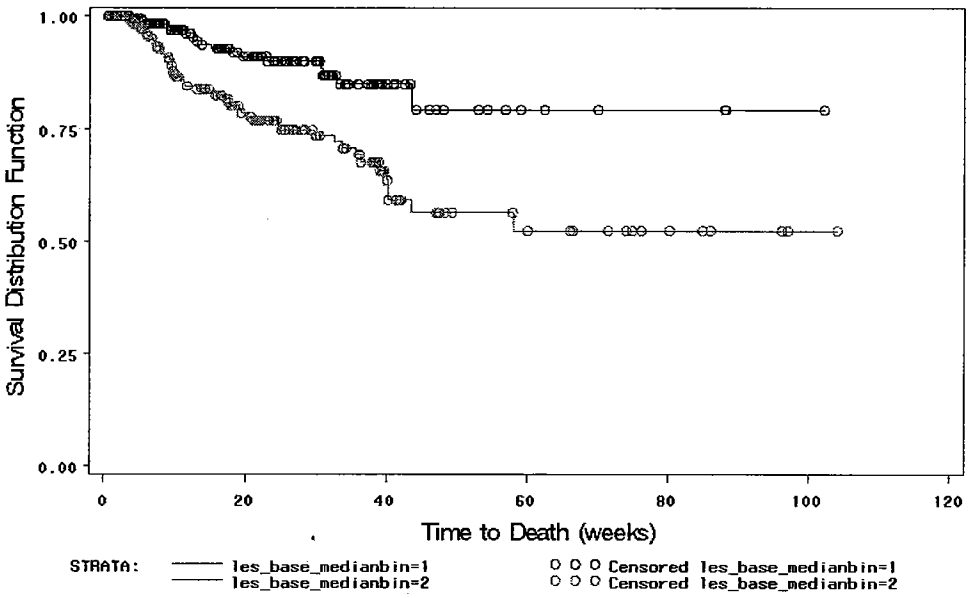

Figure PM19: Time to death for GIST patients classified into 2 groups based on a median split of baseline tumor size. Patients with smaller baseline tumor size (bin 1, black) show longer time to death (overall survival) compared to patients with larger baseline tumor size (bin 2, red).

Question: Given that baseline tumor size appears to be related to overall survival in GIST patients, is there a difference in baseline tumor size across AUCtot quartiles in GIST patients?

The following table shows the mean (SD) baseline tumor size for the placebo group and sunitinib group classified based on a median split of AUC. The data shows the substantial variability in baseline tumor sizes (~40-fold variation [12-481] across all patients). There was no obvious pattern of differences in baseline tumor sizes among groups based on AUC median split.

Table PM9: Mean (SD) baseline tumor size for placebo and sunitinib groups in GIST patients.

	Placebo n=102	Low AUC (<median) n=112	High AUC (>median) n=113
Mean (SD) [mm]	239 (164)	258 (152)	228 (135)
Range [mm]			

Baseline tumor size was plotted against AUCtot for the GIST patients. The plot does not indicate any relationship between baseline tumor size and AUCtot in the GIST patients. PROG REG of baseline tumor size vs. AUCtot was not significant (p=0.8269).

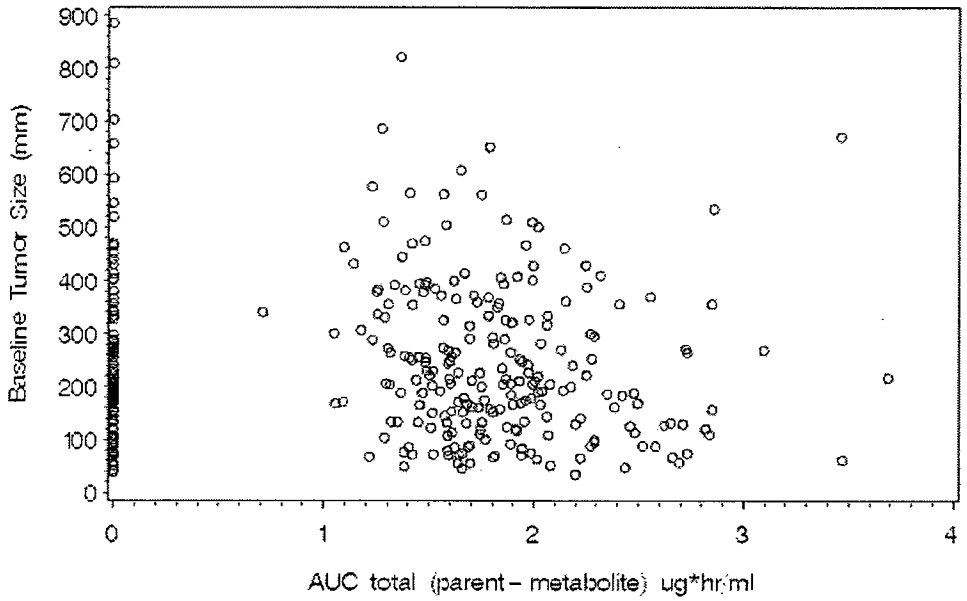

Figure PM20: Baseline tumor size as a function of total AUC (parent+metabolite). The plot illustrates the lack of difference in tumor sizes across the range of exposures in the GIST patients.

Thus, it does not appear that baseline tumor size is associated with drug exposure in GIST patients.

MRCC

Question: Does the baseline tumor size affect time to tumor progression (TTP) or overall survival (OC) in MRCC patients?

To explore the effect of baseline tumor size, the patients were classified into 4 groups, based on quartiles of baseline tumor size. Kaplan-Meier curves for TTP and OS, by baseline tumor size quartiles were plotted, as shown below. (baseline bin 1:smallest tumor size, baseline bin 4:largest tumor size)

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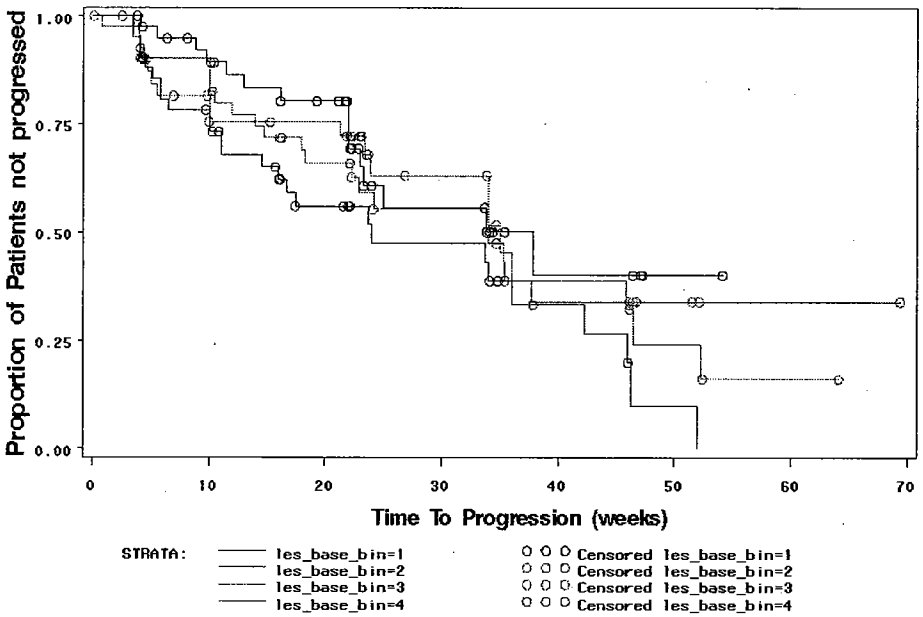

Figure PM21: Time to tumor progression for MRCC patients classified into 4 groups based on baseline tumor size quartiles.

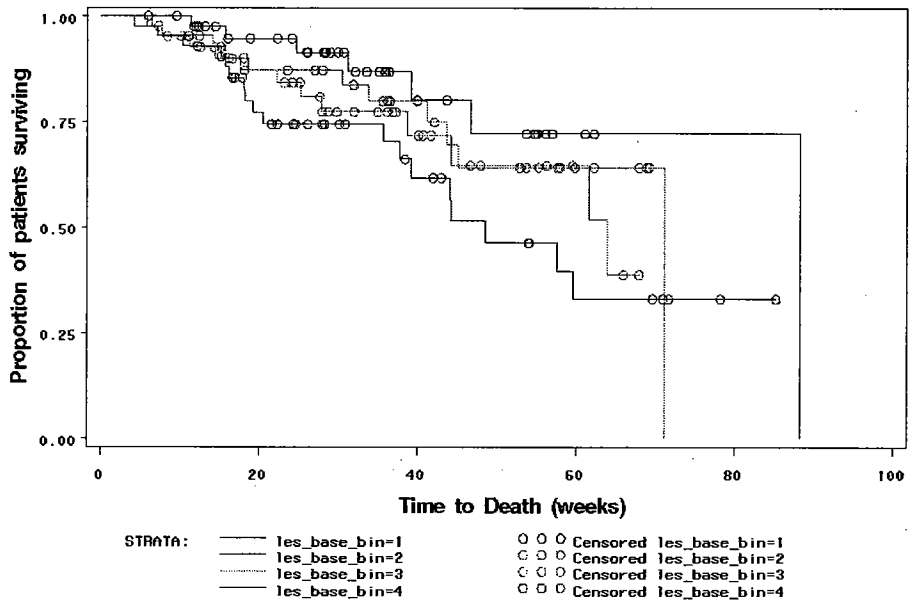

Figure PM22: Time to death (overall survival) for MRCC patients classified into 4 groups based on baseline tumor size quartiles.

The above plots suggest that patients with larger baseline tumor size (4th bin/quartile) showed trends toward a shorter TTP than patients with smaller baseline tumor size (1st quartile).
A similar pattern was seen for OS, with larger tumor size quartile patients showing shorter OS than patients with smaller baseline tumor size.

MRCC	1st Quartile Bin 1	2nd Quartile Bin 2	3rd Quartile Bin 3	4th Quartile Bin 4
Baseline Tumor size [mm]	0 – 74.5	74.5 – 117	117 – 184.5	> 184.5

The Kaplan-Meier curves were re-plotted using tumor size classified into 2 groups based on a median split, and these plots also illustrate the effect of baseline tumor size on TTP and OS in MRCC patients.

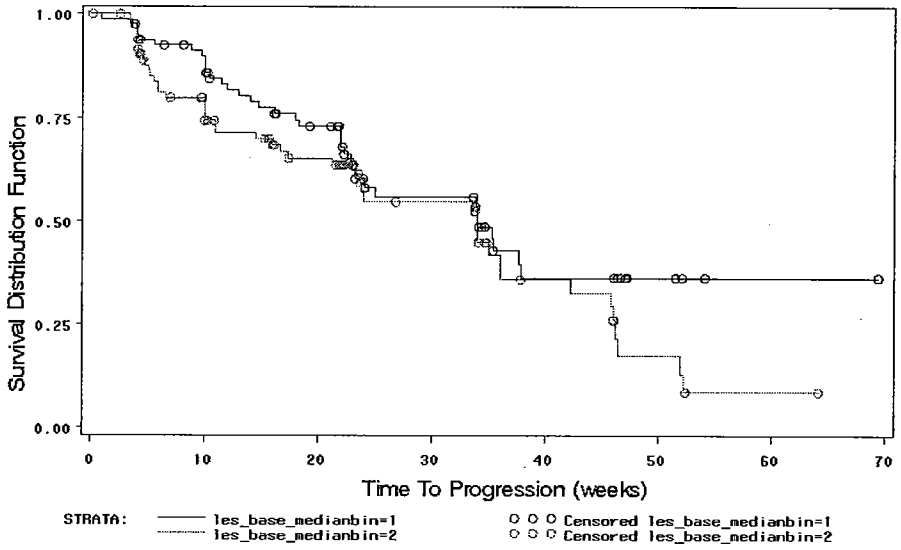

Figure PM23: Time to tumor progression for MRCC patients classified into 2 groups based on a median split of baseline tumor size.

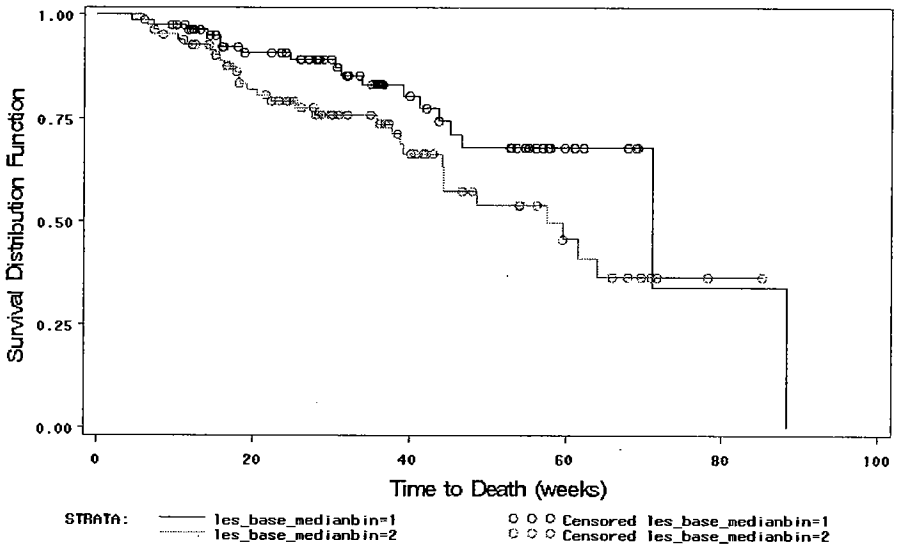

Figure PM24: Time to death (overall survival) for MRCC patients classified into 2 groups based on a median split of baseline tumor size.

Question. Given that baseline tumor size appears to be related to TTP and OS in MRCC patients, is there a difference in baseline tumor size across AUC groups in MRCC patients? [Could the apparent inverse relationship between response rate and AUC be explained by larger tumors at baseline in the patients who happened to be in the higher AUC group?]

The following table shows the mean (SD) baseline tumor size for the low and high AUC groups, classified base don a median split. The data shows the substantial variability in baseline tumor sizes (~40-fold variation [12-481 mm] across all patients). There was no obvious pattern of differences in baseline tumor sizes between the AUC groups.

Table PM10: Mean (SD) baseline tumor size for sunitinib groups, classified based on exposure, in MRCC patients.

	Low AUC n=74	High AUC n=74
Mean (SD) [mm]	135 (78)	141 (95)
Range [mm]		

Also, baseline tumor size was plotted against AUCtot for the MRCC patients. The plot did not indicate any relationship between baseline tumor size and AUCtot in the MRCC patients. PROG REG of baseline tumor size vs. AUCtot was not significant (p=0.5134).

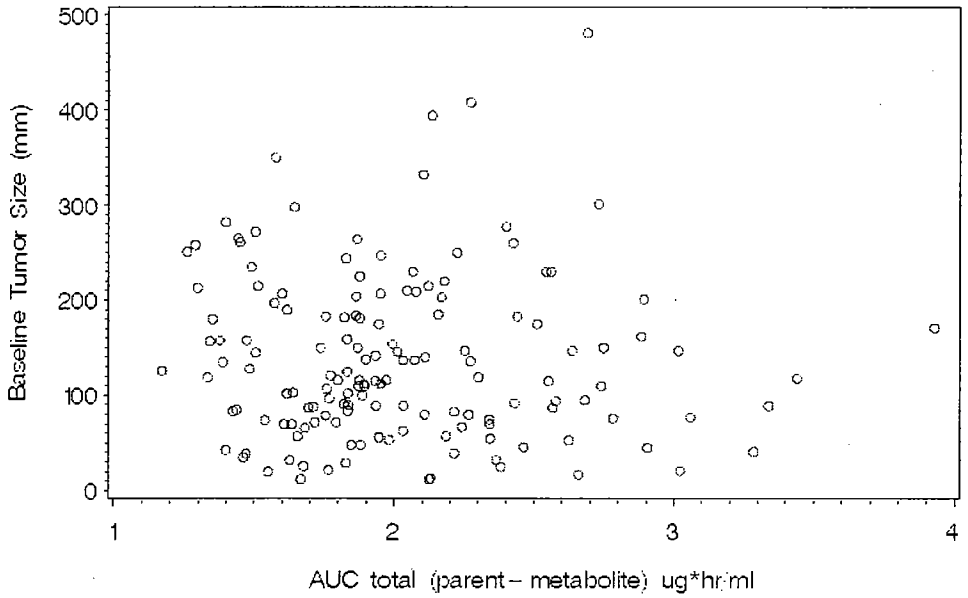

Figure PM25: Baseline tumor size as a function of total AUC (sunitinib+SU012662). The plot illustrates the lack of difference in tumor sizes across the range of exposures in the MRCC patients.

Thus, it does not appear that baseline tumor size is associated with drug exposure, and therefore does not appear to explain the apparent inverse relationship between response rates and exposure in the MRCC patients.

D. E-R for changes in tumor size during treatment.

GIST

Question: Is there an effect of AUC on change in tumor size in GIST patients?

Three measures of change in tumor size were examined: 1) the smallest absolute tumor size during the phase of the "true" or best overall RECIST response, 2) the largest absolute change in tumor size relative to baseline during the phase of the "true" or best overall RECIST response, and 3) the largest percent change in tumor size relative to baseline during the phase of the "true" or best overall RECIST response. The measures of change were only assessed during the phase of the best overall response to ensure that the absolute and percent changes in tumor size were truly reflective of the best overall response obtained for each patient (since the overall response by RECIST depends on changes in tumor size and also on changes in non-target lesions and occurrence of new lesions).
For this measure, the more negative the percent change from baseline, the larger the reduction in tumor size.
Each measure was plotted against AUC total (parent+metabolite). The following graphs show the plots and the best-fitting linear regression line.

- The smallest absolute tumor size was not significantly associated with AUC.
- The absolute change in tumor size was significantly associated with AUC ($p=0.0001$, $r^2=0.1446$). The baseline tumor size was a significant covariate in the model ($p=0.017$) and increased the r^2 to 0.1646.
- The percent change in tumor size during the "best" overall response was significantly related to AUC in these patients ($p=0.0001$, $r^2=0.1184$). The baseline tumor size was not a significant covariate in this model.
- As expected, the slope of this graph was positive, indicating that lower AUCs are associated with less negative percent changes in tumor size, and higher AUCs are associated with more negative percent changes in tumor size.

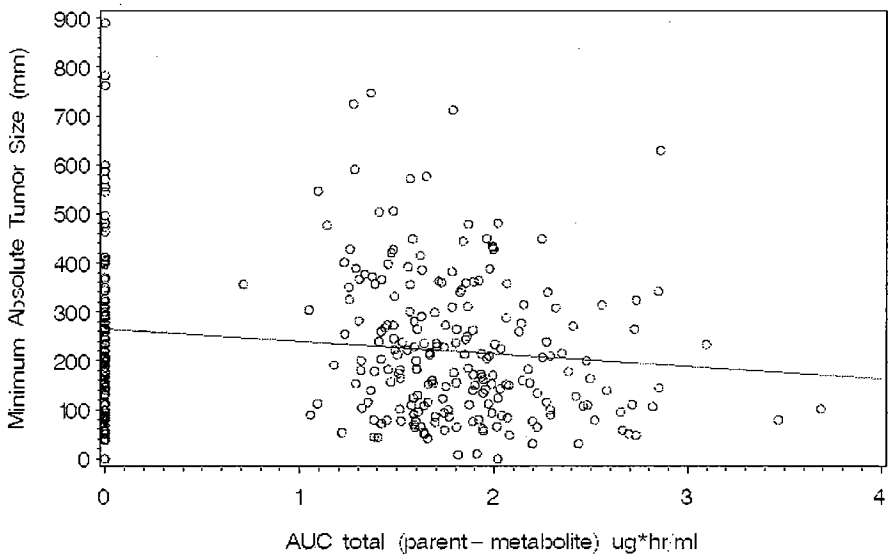

Figure PM26: Smallest Absolute tumor size post-treatment as a function of total AUC (parent+metabolite) in GIST patients. Straight line shows the regression line for the significant, although modest relationship.

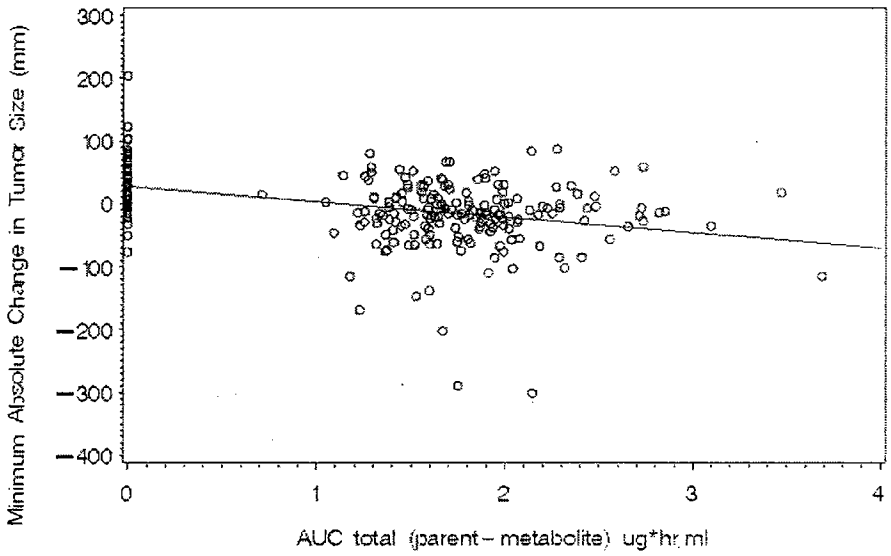

Figure PM27: Largest change in absolute tumor size post-treatment as a function of total AUC (parent+metabolite) in GIST patients. Straight line shows the regression line for the significant, although modest relationship.

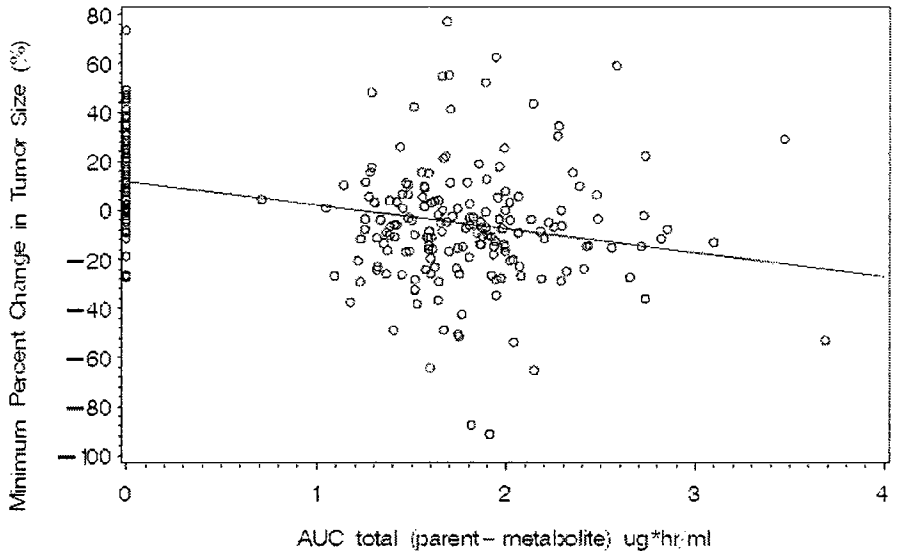

Figure PM28: Largest percent change in tumor size post-treatment as a function of total AUC (parent+metabolite) in GIST patients. Straight line shows the regression line for the significant, although modest relationship.

In summary, these findings in the GIST patients are consistent with the exposure-response relationship between partial response rates and exposure as well as the longer time to tumor progression seen in the patients in the highest AUC quartile.

Question: Is there a relationship between changes in tumor size and time to tumor progression (TTP) and between changes in tumor size and overall survival (OS) in GIST patients?

To explore the relationship between changes in tumor size and TTP and changes in tumor size and OS, the GIST patients were classified into 4 groups, based on quartiles of percent change in tumor size. Kaplan-Meier curves for TTP and OS, by change in tumor size quartiles were plotted. As there were 2 treatment groups, data were plotted separately for placebo (tmt=0) and active (tmt=50) groups.

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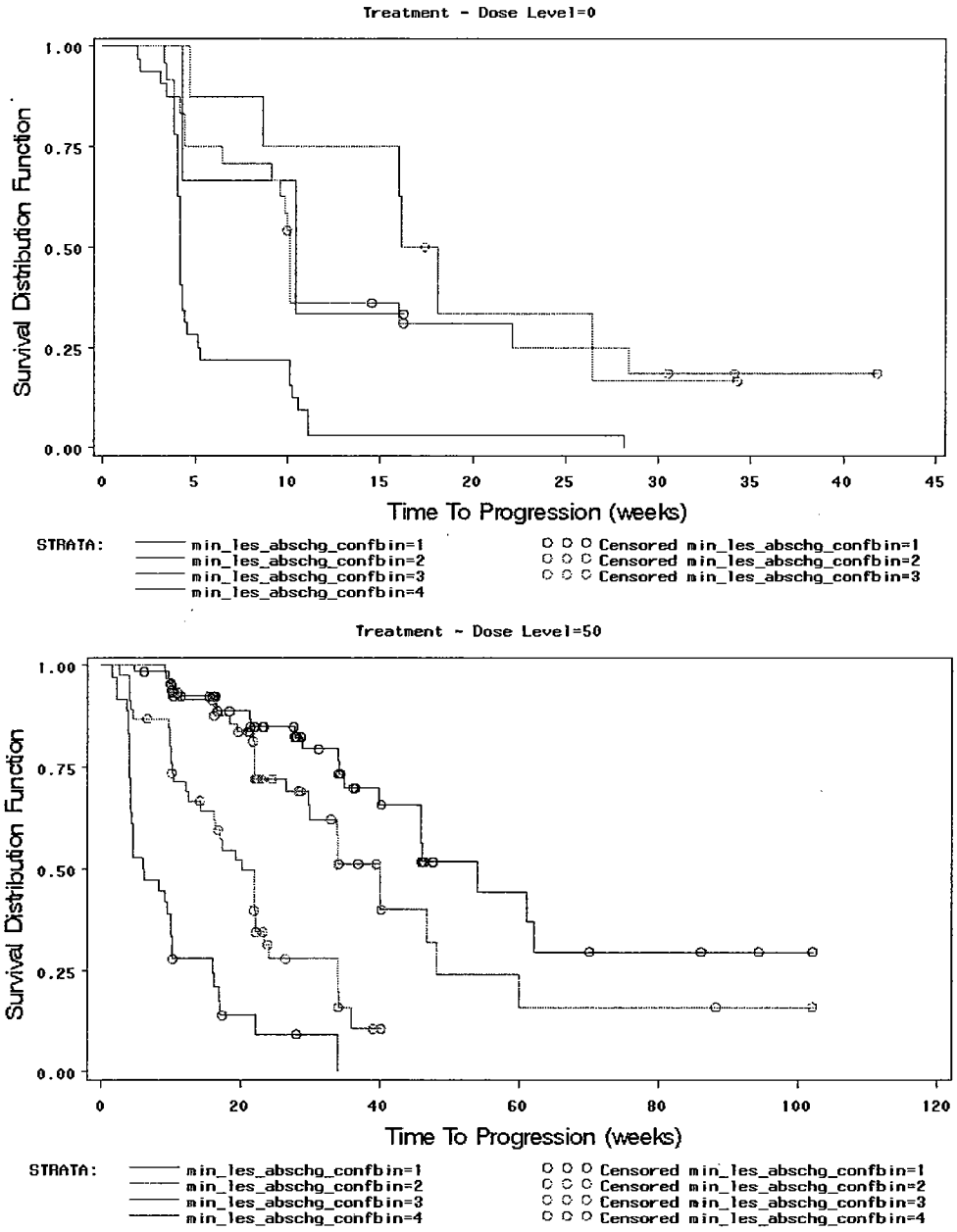

Figure PM29a: Time to progression in GIST patients following placebo (upper panel) and 50 mg QD sunitinib (lower panel), classified into 4 groups, based on magnitude of ***absolute change in tumor size*** *during treatment. Patients with the most negative % change in tumor size (bin 1, black) showed longer TTP than patients with the least negative % change in tumor size (bin 4, blue).*

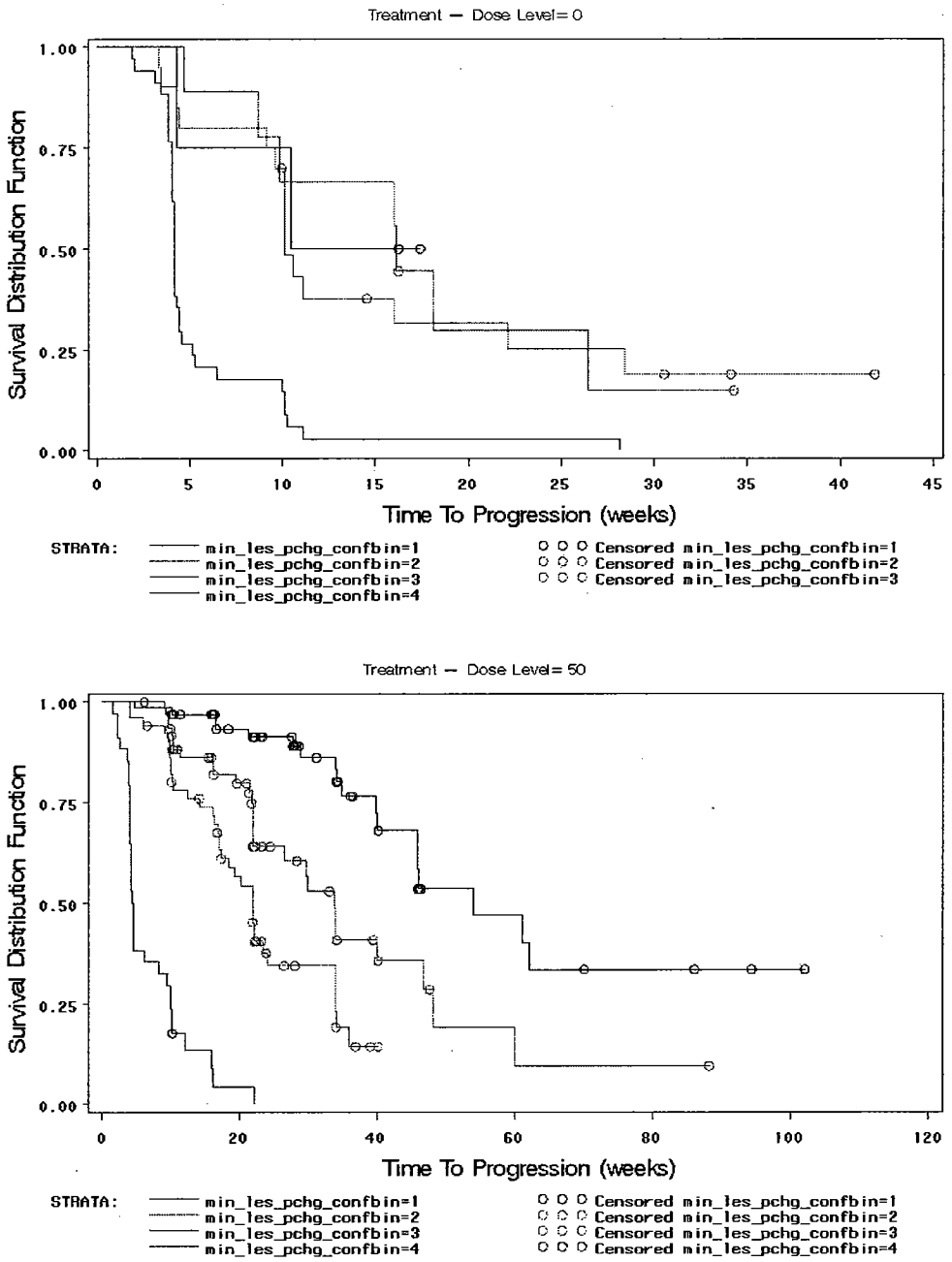

Figure PM29b: Time to progression in GIST patients following placebo (upper panel) and 50 mg QD sunitinib (lower panel), classified into 4 groups, based on magnitude of ***percent change in tumor size*** *during treatment. Patients with the most negative % change in tumor size (bin 1, black) showed longer TTP than patients with the least negative % change in tumor size (bin 4, blue).*

The above plots show that patients with larger changes in tumor size (more negative change), which correspond to the first quartile (black curve in above plots) have longer TTP compared

with patients with smaller changes in tumor size (less negative change) corresponding to the fourth quartile (blue curve). This is seen for both placebo and drug treated groups.

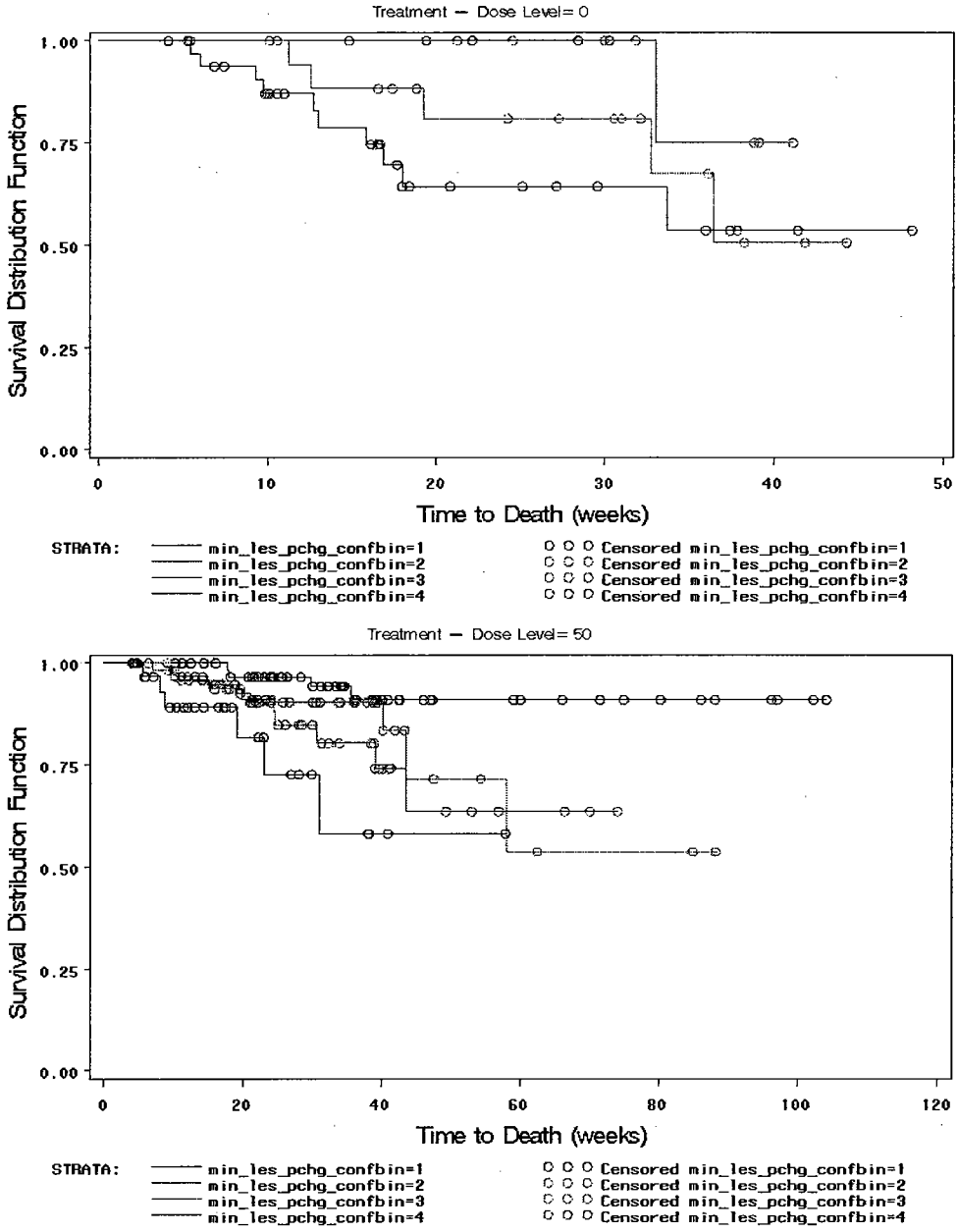

Figure PM30: Time to death (overall survival) in GIST patients following placebo (upper panel) and 50 mg QD sunitinib (lower panel), classified into 4 groups, based on magnitude of percent change in tumor size during treatment. Patients with the most negative % change in tumor size (bin 1, black) showed longer survival than patients with the least negative % change in tumor size (bin 4, blue).

The above plots show that patients with larger changes in tumor size (more negative change), which correspond to the first quartile (black curve in above plots) have longer OS compared with

patients with smaller changes in tumor size (less negative change) corresponding to the fourth quartile (blue curve). This was seen for both placebo and drug treated groups.

MRCC

Question: Is there an effect of AUC on change in tumor size in MRCC patients?

Given the apparent inverse relationship between exposure and response rates (categorical variable) in MRCC patients, it was of interest to know the effect of exposure directly on actual changes in tumor size (continuous variable).

Three measures of change in tumor size were examined: 1) the smallest absolute tumor size during the phase of the "true" or best overall RECIST response, 2) the largest absolute change in tumor size relative to baseline during the phase of the "true" or best overall RECIST response, and 3) the largest percent change in tumor size relative to baseline during the phase of the "true" or best overall RECIST response. The measures of change were only assessed during the phase of the best overall response to ensure that the absolute and percent changes in tumor size were truly reflective of the best overall response obtained for each patient (since the overall response by RECIST depends on changes in tumor size and also on changes in non-target lesions and occurrence of new lesions).

For this measure, the more negative the percent change from baseline, the larger the reduction in tumor size.
Each measure was plotted against AUC total (parent+metabolite). The following graphs show the plots and the best-fitting linear regression line.

Results:

- The smallest absolute tumor size was not significantly associated with AUC.
- The absolute change in tumor size was also not significantly associated with AUC ($p=0.4734$). The baseline tumor size was a significant predictor of the absolute change in tumor size ($p=0.0001$, $r^2=0.3028$.
- The percent change in tumor size during the "best" overall response was not significantly related to AUC in these patients. The baseline tumor size was also not a significant covariate in this model.

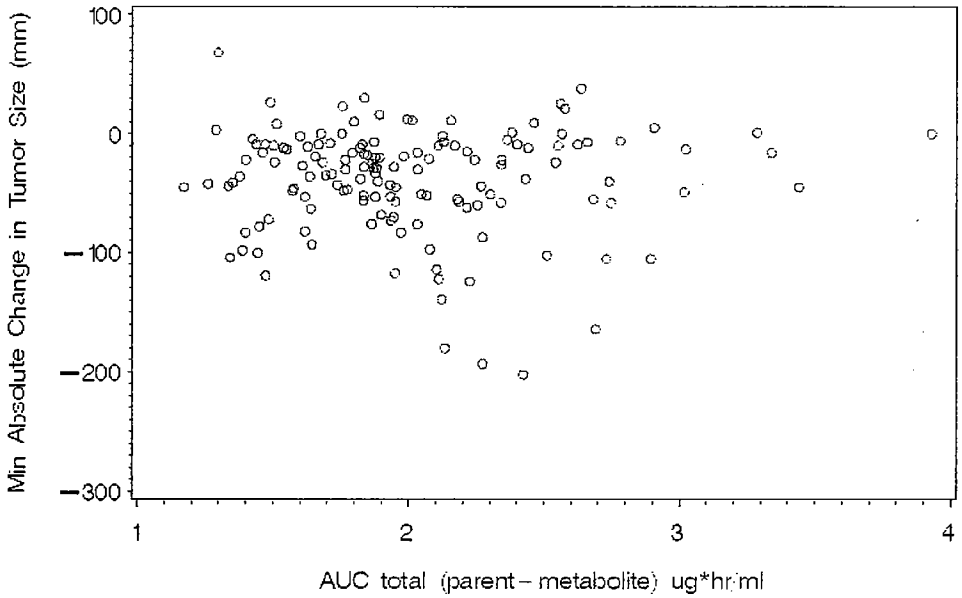

Figure PM31: Smallest Absolute tumor size post-treatment as a function of total AUC (parent+metabolite) in MRCC patients, showing the lack of significant association between exposure and the smallest absolute tumor size.

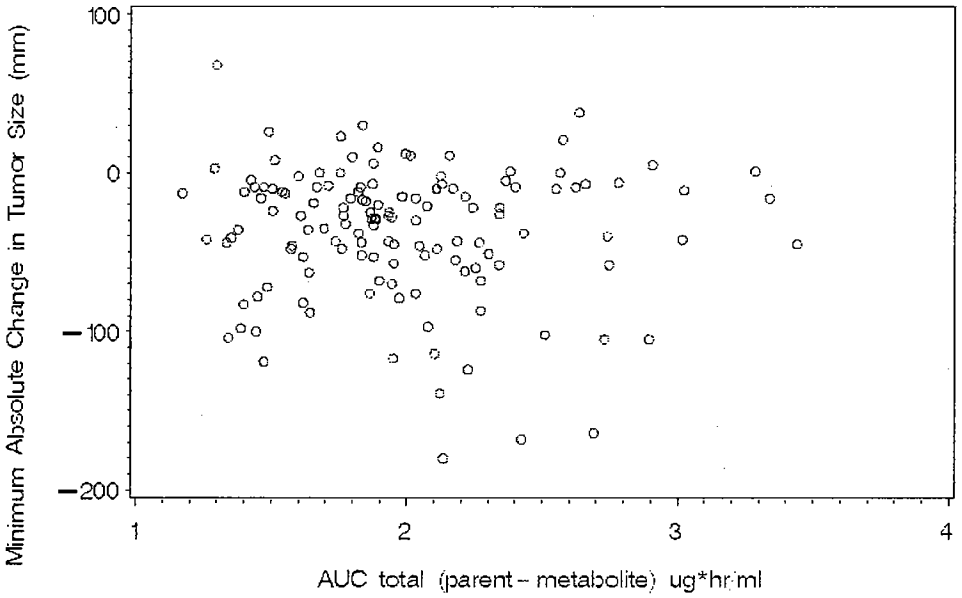

Figure PM32: Largest absolute change in tumor size post-treatment as a function of total AUC (parent+metabolite) in MRCC patients, showing the lack of significant association between exposure and largest absolute change in tumor size.

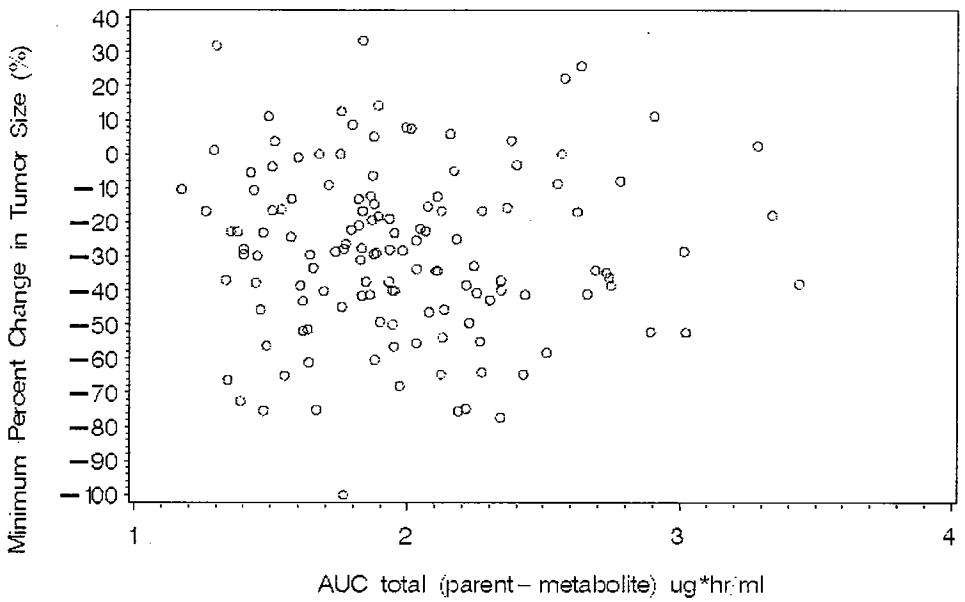

Figure PM33: Largest percent change in tumor size post-treatment as a function of total AUC (parent+metabolite) in MRCC patients, showing the lack of significant association between exposure and largest percent change in tumor size.

These findings are consistent with the observed apparent inverse relationship between partial response rates (categorical response defined by RECIST criteria) and exposure. This is also consistent with the longer time to tumor progression seen in the patients in the highest AUC quartiles.

Question: Is there a relationship between changes in tumor size and time to tumor progression (TTP), and between changes in tumor size and overall survival (OS) in MRCC patients?

To explore the relationship between changes in tumor size and TTP and changes in tumor size and OS, the patients were classified into 4 groups, based on quartiles of percent change in tumor size. Kaplan-Meier curves for TTP and OS by change in tumor size quartiles were plotted.

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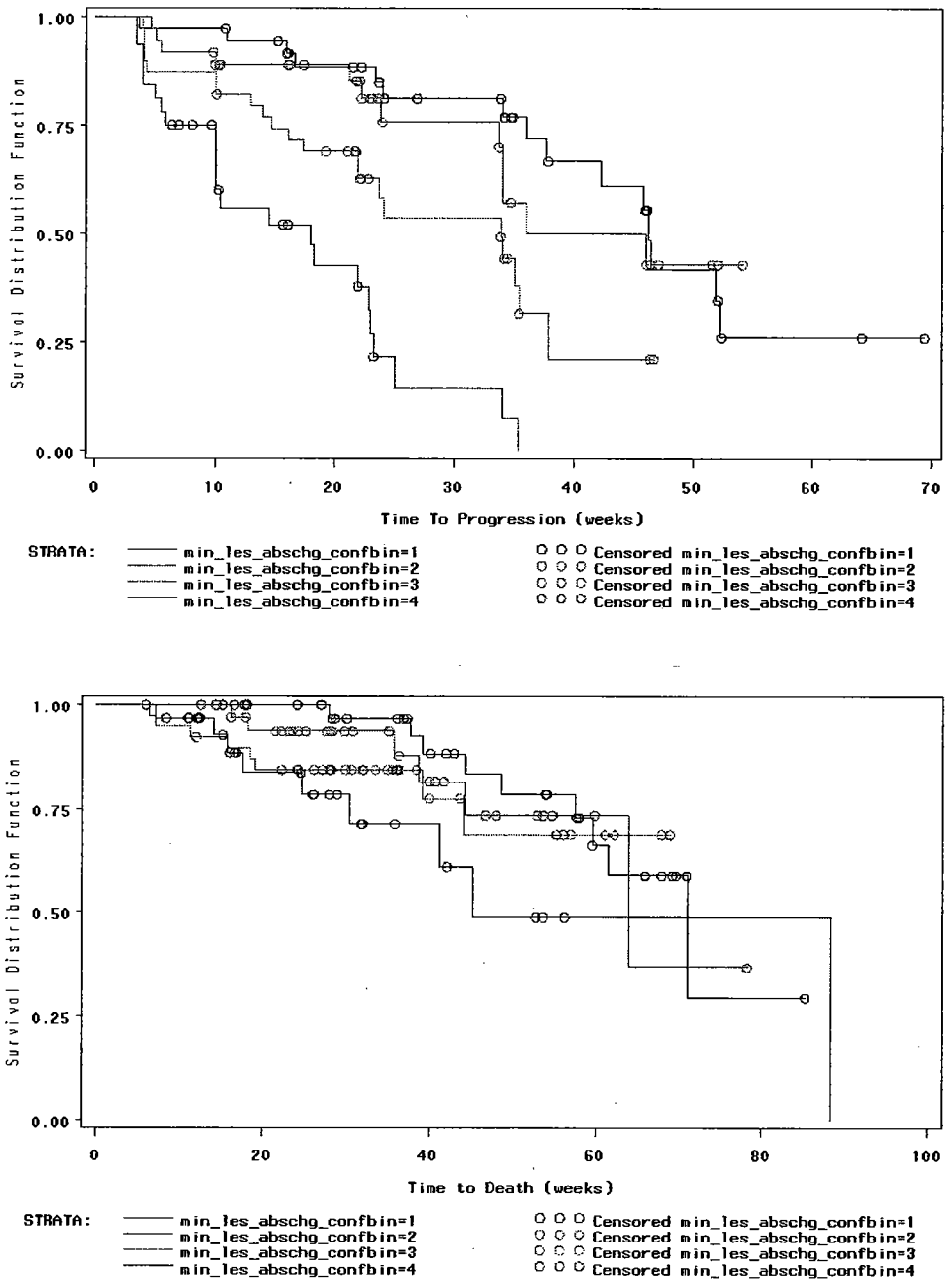

Figure PM34a: Time to progression (upper panel) and time to death (lower panel) in MRCC patients, classified into 4 groups, based on magnitude of ***absolute change in tumor size*** *during treatment. Regardless of exposure, patients with the most negative % change in tumor size (bin 1, black) showed longer survival than patients with the least negative % change in tumor size (bin 4, blue).*

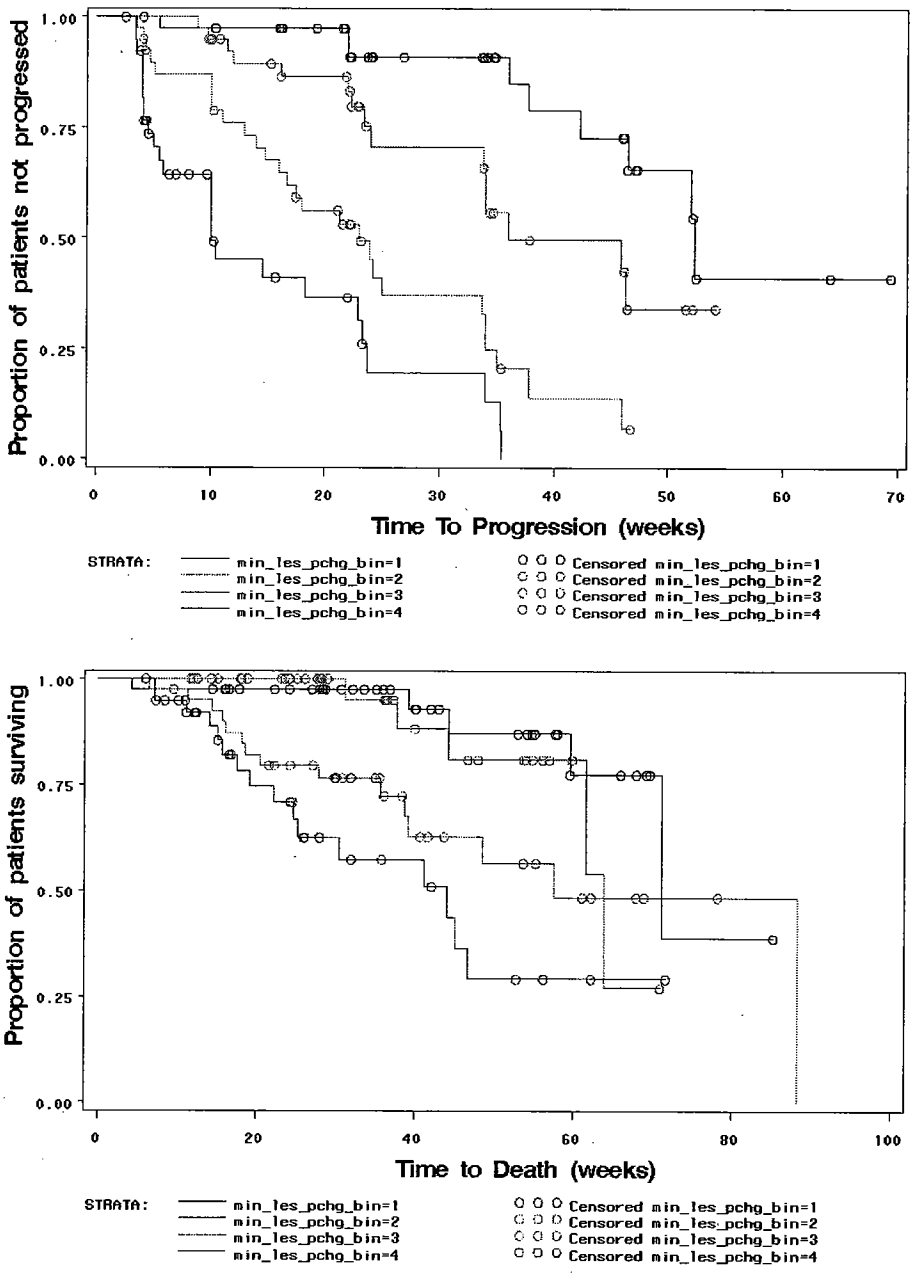

Figure PM34b: Time to progression (upper panel) and time to death (lower panel) in MRCC patients, classified into 4 groups, based on magnitude of ***percent change in tumor size*** *during treatment. Regardless of exposure, patients with the most negative % change in tumor size (bin 1, black) showed longer survival than patients with the least negative % change in tumor size (bin 4, blue).*

The above plots show that patients with larger changes in tumor size (more negative change), which correspond to the first quartile (black curve in above plots) have longer TTP and OS compared with patients with smaller changes in tumor size (less negative change) corresponding to the fourth quartile (blue curve).

II. E-R FOR TOXICITY OF SUNITINIB

Question: Are the following toxicities seen with sunitinib exposure-dependent?

i) fatigue
ii) nausea
iii) vomiting
iv) neutropenia
v) thrombocytopenia
vi) anemia
vii) pancreatic dysfunction
viii) hypertension
ix) LVEF dysfunction

The toxicity data was evaluated for all the above adverse events, using logistic regression. The frequency of severe grade 3/4 toxicity for all the above measures (except nausea and vomiting where all grades were included and hypertension where grade 2/3 toxicity was used) was modeled as a function of AUCtotal (parent+metabolite). The effect of sex, tumor type (GIST, MRCC, solid tumors) and ECOG score was also examined in these models.

Additional analyses were performed for fatigue, absolute neutrophil counts, blood pressure and LVEF. Each of these measures was analyzed as continuous variables as functions of exposure (AUC or trough concentrations) along with covariates including sex, ECOG score and tumor type. These analyses are described below (III.b).

The following table gives a summary of the results.

Table PM11: Frequency of major severe grade 3/4 toxicities with sunitinib and odds ratio for AUC based on logistic regression analysis.

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

The following figures show the probability of severe (grade 3/4) toxicity as a function of AUCtot.

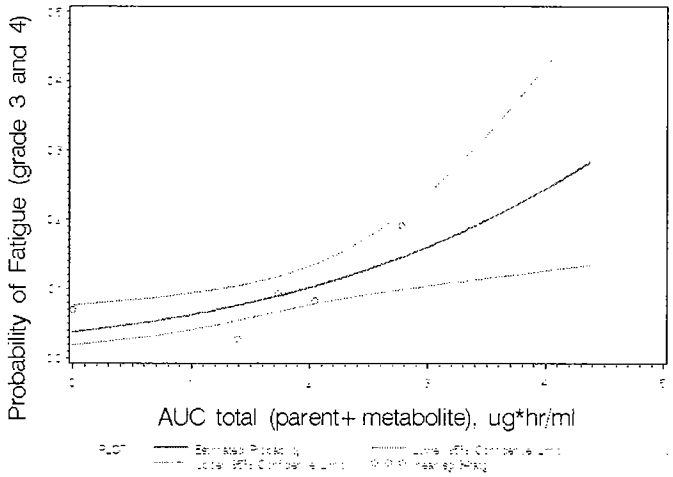

Figure PM35: Probability of severe grade 3/4 fatigue vs. AUCtotal (parent+metabolite).

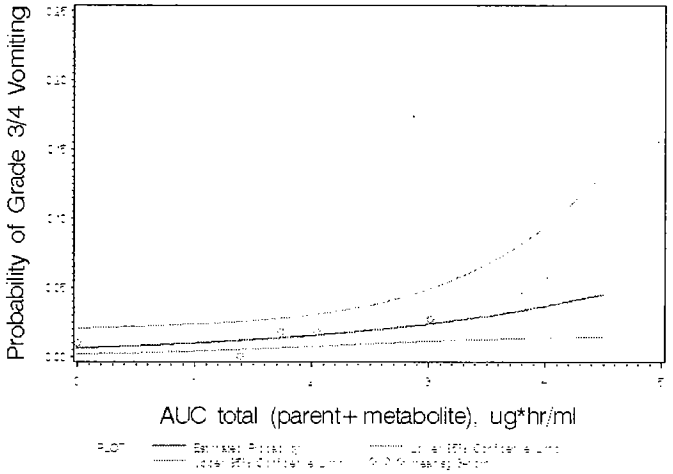

Figure PM36: Probability of grade 3/4 vomiting vs. AUCtotal (parent+metabolite).

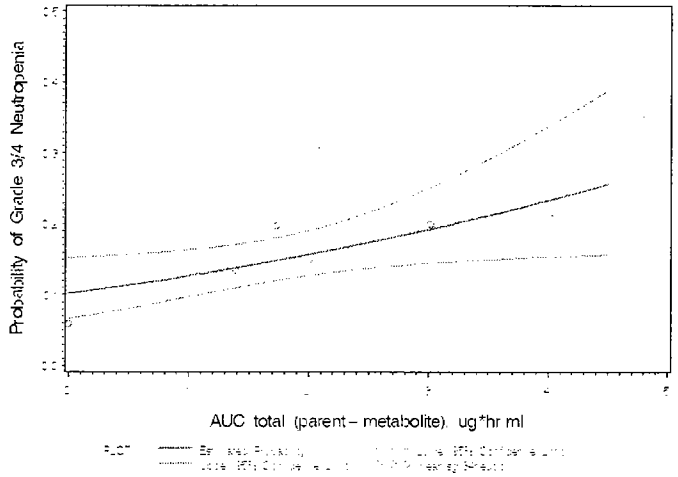

Figure PM37: Probability of grade 3/4 neutropenia vs. AUCtotal (parent+metabolite).

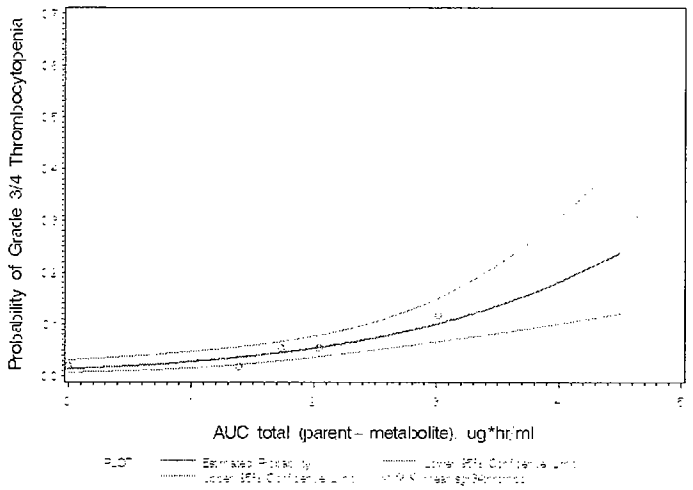

Figure PM38: Probability of grade 3/4 thrombocytopenia vs. AUCtotal (parent+metabolite).

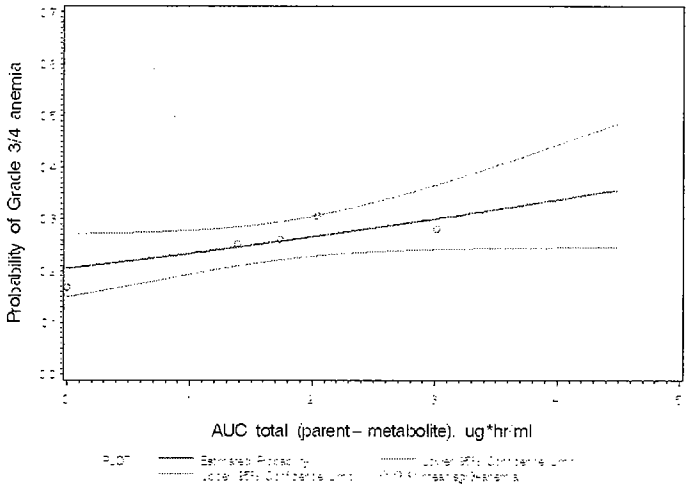

Figure PM39: Probability of grade 3/4 anemia vs. AUCtotal (parent+metabolite).

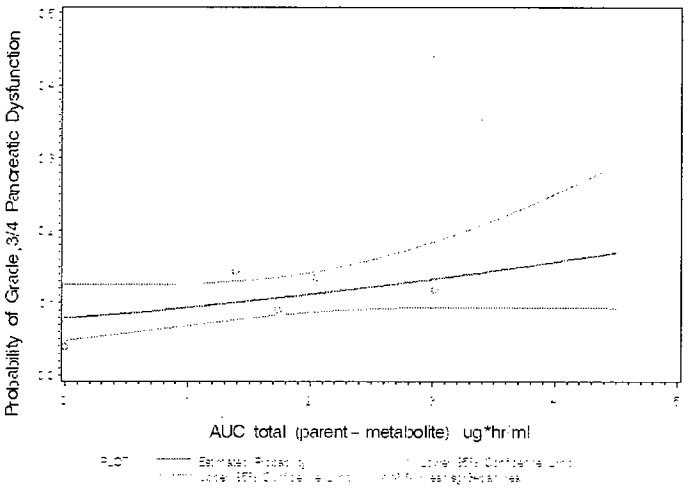

Figure PM40: Probability of grade 3/4 pancreatic dysfunction vs. AUCtotal (parent+metabolite).

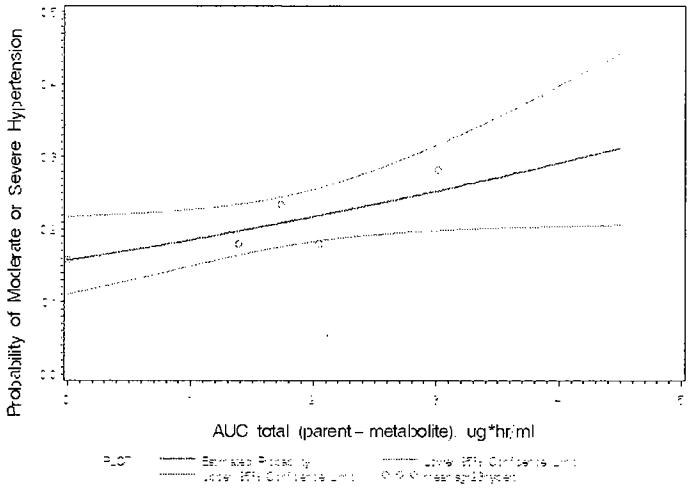

Figure PM41: Probability of grade 2/3 hypertension vs. AUCtotal (parent+metabolite).

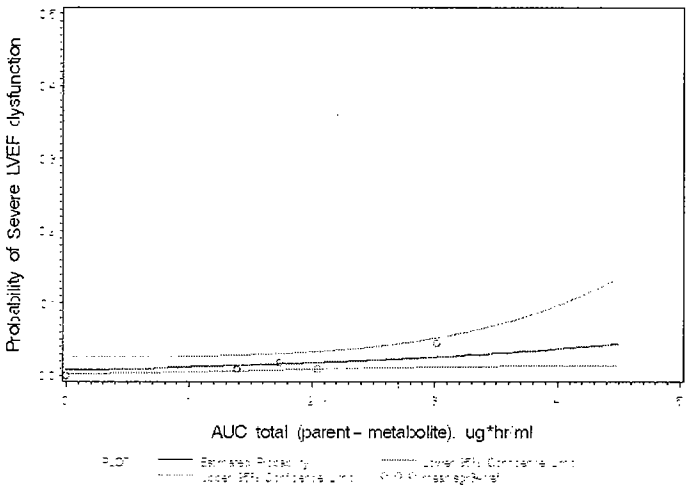

Figure PM42: Probability of grade 3/4 LVEF dysfunction vs. AUCtotal (parent+metabolite).

Summary:
The above analyses clearly demonstrated exposure-related toxicity for most of the measures of toxicity measures evaluated. To better understand the E-R relationship for these measures, the blood pressure and LVEF were evaluated as continuous variables in additional E-R relationships (see below).

Question: Is there a quantitative E-R relationship for the following measures of toxicity: fatigue grade, absolute neutrophil counts, blood pressure and LVEF?

In addition to the analyses described above, fatigue grade, absolute neutrophil counts, blood pressure and LVEF were also analyzed using a different approach. Each of these measures was analyzed as continuous variables as a function of exposure (AUC or trough concentrations) along with covariates including sex, ECOG score and tumor type.

A. Incidence and severity of fatigue as a function of exposure.

As indicated above, fatigue was one of the most prevalent of the toxicities seen following sunitinib. In early studies, fatigue was a dose-limiting toxicity. Fatigue was scored on an ordinal scale from 0 to 4. Repeated-measures logistic regression was used to analyze the data. A two-part mixture model was used to account for the high proportion of observations of no event. Two logit probability models were used together to describe the data.

The first model describes the incidence of fatigue as a function of exposure:

$$\text{logit } P(Y>0) = INT + TT + SLP1*\text{exposure}$$

where INT: intercept
TT: tumor type
SLP1: slope of logit relationship for fatigue incidence with exposure

The second model is a standard logit probability model for repeated measurements, which describes the probability of exceeding a given fatigue grade, i.e. severity, given that the patient experienced fatigue:

$$\text{logit } P\ (Y>=m \mid Y>0) = B_m + Pmax*(1-\exp(-K*t) + SLP2*\text{exposure}$$

where B_m: intercept, i.e., fatigue rate for severity=m at time 0 with no drug.
Pmax: maximum placebo response
K: rate constant for placebo response
SLP2: slope of logit relationship for fatigue severity with exposure

The exposure measures considered were ISTR (binomial variable indicating presence of active treatment (ISTR=1) or placebo (ISTR=0)), and total AUC (parent+metabolite).

The sponsor's model was re-run using the above-described exposure measures, under 2 conditions: incorporating only incidence, i.e., the incidence of fatigue (but not the severity of fatigue) modeled as a function of exposure, and then incorporating both incidence and severity models. The results are shown in the table below.

Table PM12: Results of repeated measures logistic regression models fitting of fatigue data.

Model	Exposure	OBJ	Parameter SLP1	Parameter SLP2
Incidence only SLP1 estimated SLP2 = 0	ISTR	36812.775	0.461 (60%)	0
	AUCT	**36403.522**	0.446 (26%)	0
Incidence + Severity SLP1 and SLP2 estimated	ISTR	36812.747	0.461 (60%)	-0.0512 (545%)
	AUCT	36401.559	0.446 (26%)	0.145 (83%)

As the above table indicates, the final model chosen was where only the incidence of fatigue was modeled as a function of the total AUC (parent+metabolite). The severity of fatigue included an intercept term and a term characterizing the time course of placebo, but did not include a drug effect. Inclusion of a severity term and estimation of an additional parameter SLP2 did not significantly improve the fit (non-significant decrease in OBJ). The following figures shows the predicted probability for the various grades of fatigue as a function of time, based on the final model, for a typical patient on sunitinib and a typical patient on placebo.

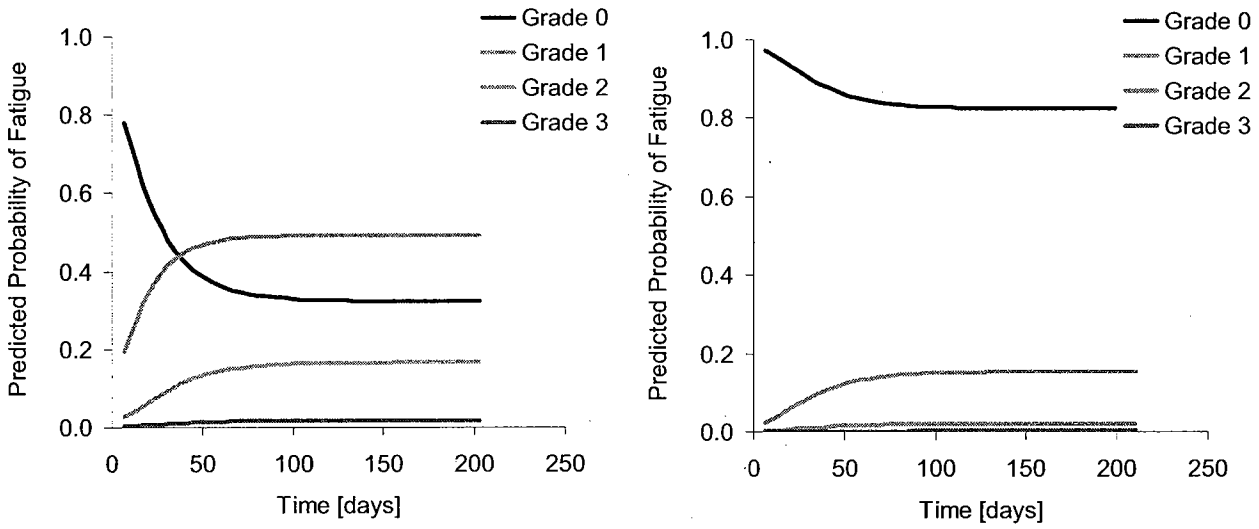

Figure PM43: Time course of predicted probability of fatigue severity, by grade (Y=0 to Y=3) for a typical patient on sunitinib (Left panel, total AUC=1.7 ug.hr/ml) and on placebo (Right panel, total AUC=0). The patient on sunitinib on the left showed a large increase in probability of grade 1 (pink curve) and grade 2 (red curve) fatigue and a decrease in the probability of no (grade 0, blue curve) fatigue with time. The patient on placebo on the right showed a small increase in probability of grade 1 fatigue and a small decrease in probability of no (grade 0) fatigue with time.

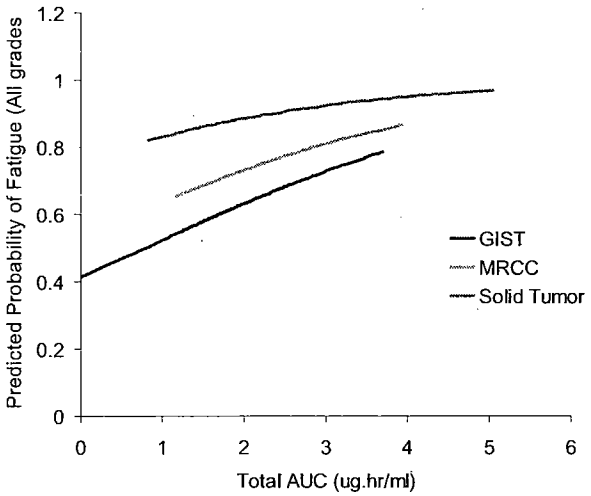

Figure PM44: Predicted probability of fatigue incidence (any grade) as a function of total AUC, by tumor type.

B. Change in absolute neutrophil count as a function of exposure.

For most patients, serial measurements of ANC were obtained across multiple cycles of exposure. To better describe the E-R relationship for neutropenia, the nadir for the ANC was modeled as a function of the AUCtot (parent+metabolite) using the following models.

Table PM13: Summary of models used in analysis of changes in ANC vs. exposure.

Number	Model	R-sq	Coefficient	P value
1	Ln(ANCnadir) = E0 + Slop•ISTRT	0.0979	ISTRT	0.0001
2	Ln(ANCnadir) = E0 + Slop•AUCtot	0.0756	AUCtot	0.0001
3	Model 2 with covariates: sex, tumor type, ECOG	0.1413	AUCtot Sex ISGIST ISMRCC ISECOG1 ISECOG2	0.0001 0.2947 0.4307 0.6667 0.0016 0.0005

Results indicate a significant relationship between ANC nadir and exposure. ECOG score was a significant covariate in this relationship. Sex and tumor type were not significant predictors. The figure below shows the observed values and predicted ANS vs. total AUC. The plot illustrates the large variability in ANC nadir and the decrease in ANC (neutropenia) with increase in exposure.

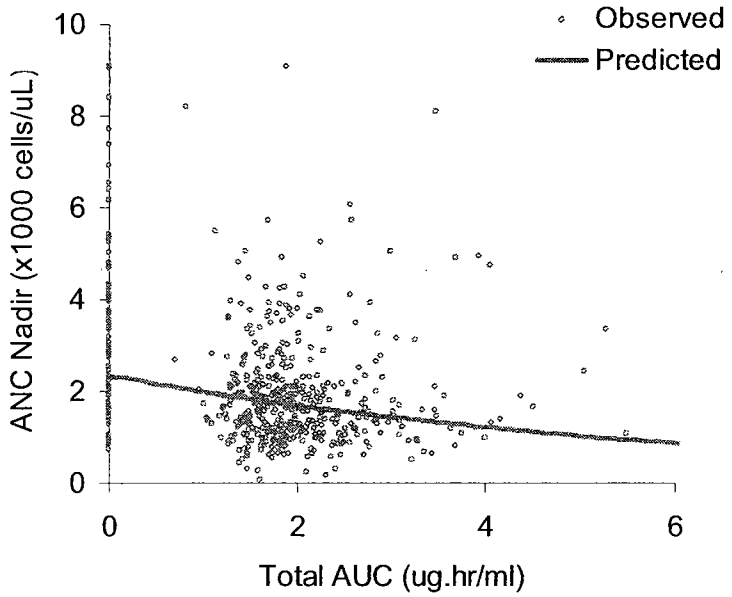

Figure PM45: ANC Nadir vs. total AUC (parent+metabolite). Solid line is from the best fitting model.

C. Changes in diastolic blood pressure as a function of exposure.

For most patients, serial measurements of blood pressure (BP) as well as trough concentrations were obtained across multiple cycles of exposure. Two approaches were used to describe the E-R relationship for hypertension:
1) Maximal change in BP from baseline vs. AUC (parent+metabolite) (one observation per individual)
2) Change in BP from baseline (CHBP) vs. trough concentrations (Ctot, parent+metabolite) (multiple obs per individual).

1) Maximal change in BP from baseline vs. AUC
The following table shows the models used and the results of the analysis.

Table PM14: Summary of models used in analysis of changes in diastolic BP vs. total AUC.

Number	Model	OBJ	Parameter				
			E0	Slop	POW	Emax	EC50
1 deltabpmax_auc_slop0	CHBP = CHBPo	3800.7	14.8				
2 deltabpmax_auc_linear	CHBP = CHBPo*(1 + Slop*AUCT)	**3788.6**	13.2	1.04			
3 deltabpmax_auc_power	CHBP = CHBPo*(1 + Slop*AUCT^{POW})	3788.6	13.2	1.11	0.93		
4 deltabpmax_auc_emax	CHBP = CHBPo*(+ Emax*AUCT/(EC50+AUCT)	3788.4	13.2			17.1	13.7

where:
CHBPo: changes in diastolic BP not due to drug (placebo effect)
AUCT: AUCtot for parent+metabolite
Slop: slope of CHBP vs. AUCT relationship
POW: power function value
Emax: maximum change in BP
EC50: AUCT corresponding to half-Emax

Inclusion of exposure in the model significantly reduced the objective function value (Model 1 vs. 2). Incorporating an exponent for the AUC did not improve the fit (no decrease in the OBJ). Using an Emax model also did not improve the fit.
The final model chosen was the linear model, although the goodness-of-fit plots (observed vs. predicted) indicated a large degree of variability in the dependent variable and a rather poor fit. Thus, the analysis of maximal change in BP vs. AUC indicated a rather weak relationship with very little value in predicting changes in BP at various levels of exposure.

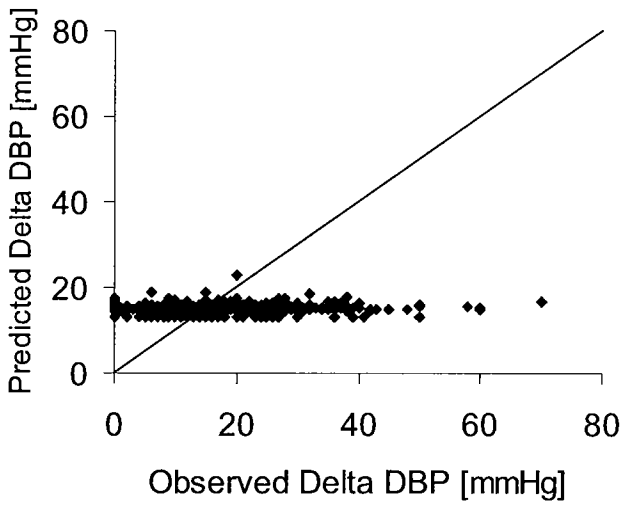

Figure PM46: Observed vs. predicted plot for maximum change in diastolic blood pressure. Line represents unity.

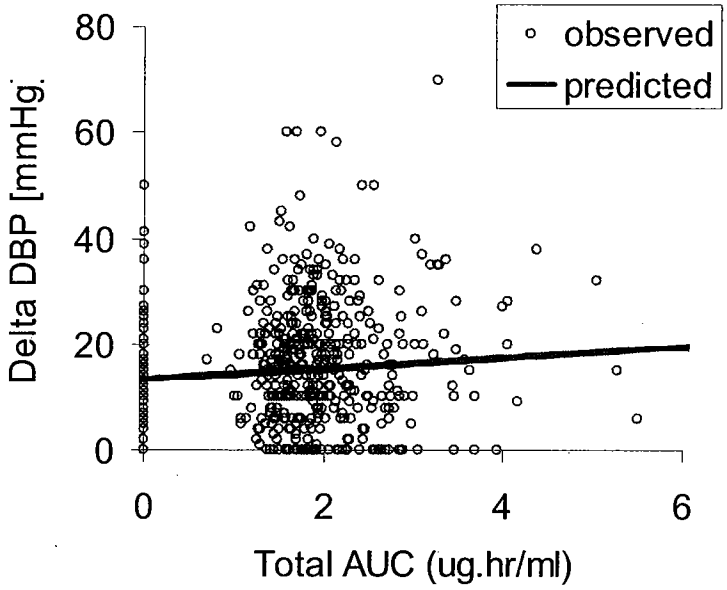

Figure PM47: Maximum change in diastolic blood pressure vs. total AUC across patients. Line represents line of best fit. Plot illustrates the substantial variability in response and the modest relationship with exposure.

2) Change in BP from baseline (CHBP) vs. trough concentrations

The following table shows the models used and the results of the analysis.

Table PM15: Summary of models used in analysis of changes in diastolic BP vs. combined trough concentrations (parent+metabolite).

Number	Model	OBJ	Parameter				
			E0	Slop	POW	Emax	EC50
1 chbp_ctot_slop0	CHBP = CHBPo	26473.715	5.07				
2 chbp_ctot_linear2	CHBP = CHBPo • (1 + Slop•CTOT)	**26126.969**	3.13	2.36			
3 chbp_ctot_power2	CHBP = CHBPo • (1 + Slop•$CTOT^{POW}$)	26210.026	2.58	4.42	3.09		
4 chbp_ctot_emax2	CHBP = CHBPo • (1 + Emax•CTOT/(EC50+CTOT))	26182.611	3.15			2.4	1.09

where:
CHBPo: changes in DBP not due to drug (placebo effect)
Slop: slope of CHBP vs. CTOT (CTparent+CTmetabolite) relationship
CTOT: Ctrough for parent+metabolite
POW: power function value
Emax: maximum change in BP
EC50: CTOT corresponding to half-Emax

Inclusion of exposure in the model significantly reduced the objective function value (Model 1 vs. 2). Incorporating an exponent for the AUC worsened the fir. Also, using an Emax model did not give a lower OBJ compared to the linear model.

The final model chosen was the linear model. Goodness of fit plots indicate a fairly robust relationship. Individual changes in BP vs. trough concentrations are shown for several patients and indicate a shallow but good fit. The model suggests that an average total trough concentration of 0.075 ug/ml (total trough level observed in the clinical studies) would result in a 3.3 mmHg increase in diastolic BP (for reference, the model predicts that no treatment would result in 3.13 mmHg increase in BP). A doubling of trough levels to 0.15 ug/ml would result in a 3.5 mmHg increase in BP. While these relationships are statistically significant, the predicted changes are lower than changes in BP that would be considered clinical significant (i.e., 5 mmHg). Thus, no specific instructions or dosing recommendations can be made with regard to changes in BP induced by sunitinib.

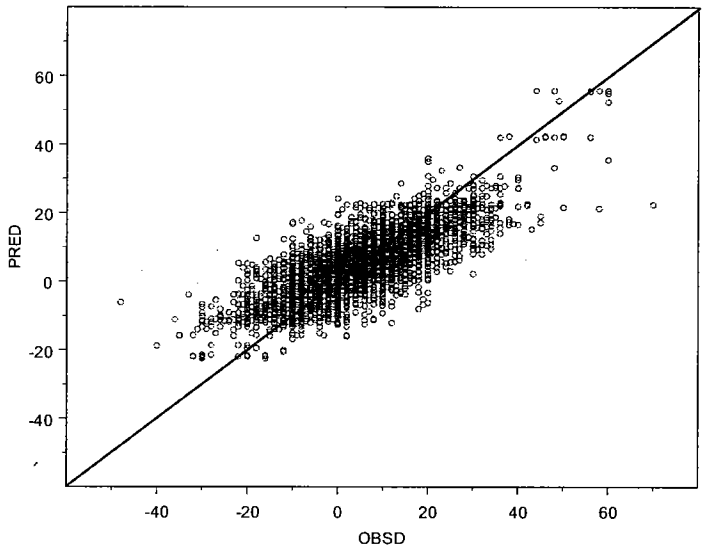

Figure PM48: Observed vs. predicted plot for change in diastolic blood pressure. Line represents unity.

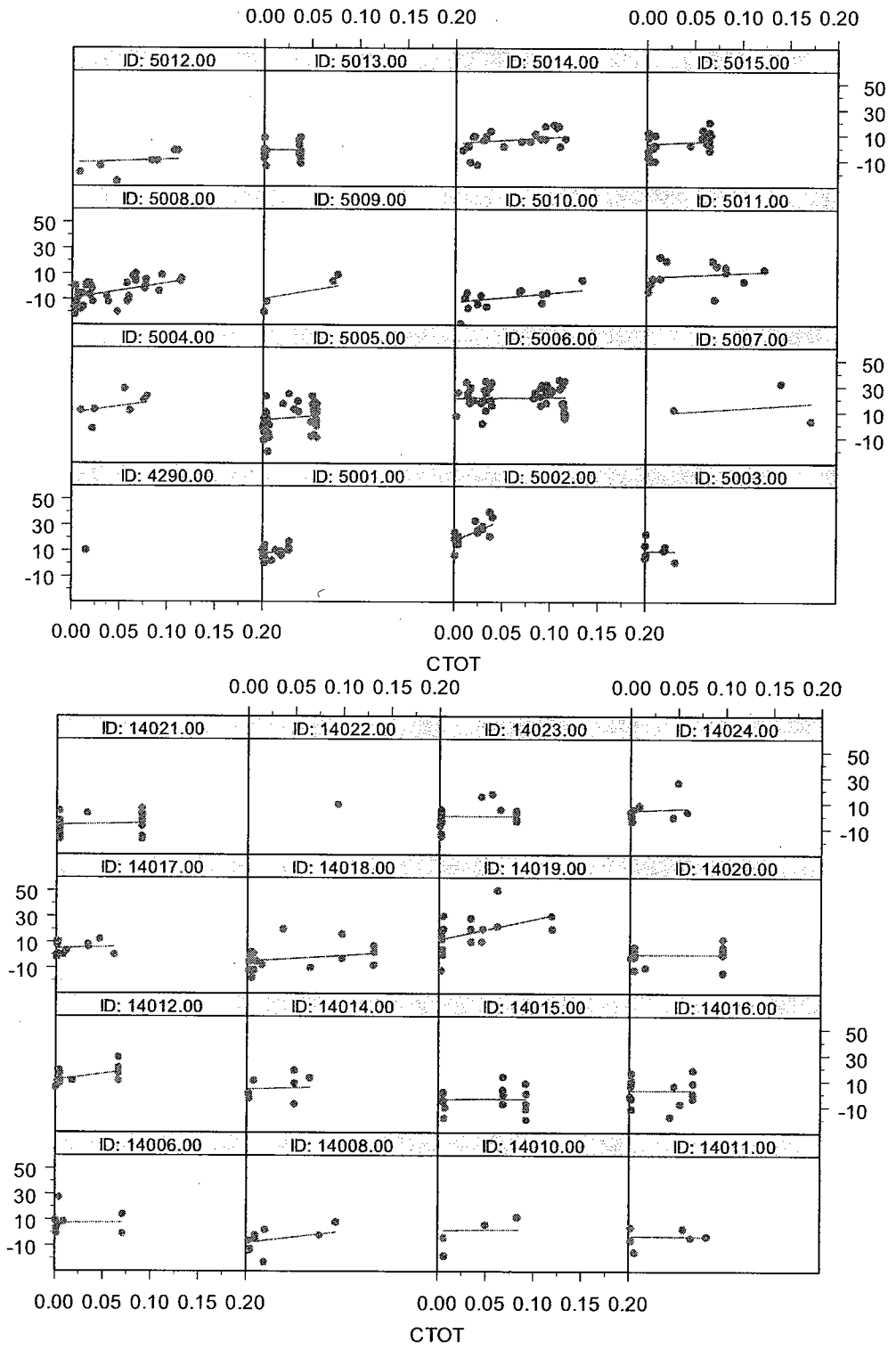

Figure PM49: Change in diastolic blood pressure as a function of total trough concentrations (parent+metabolite) for a sample of patients. Red circles: observed data, line: best-fit regression line.

D. Changes in Left Ventricular Ejection Fraction (LVEF) as a function of exposure.

Severe decrease in LVEF was observed in 6/639 patients following sunitinib in both GIST and MRCC patients. While the incidence of severe LVEF was not significantly associated with exposure (see results of logistic regression above), the relationship between individual changes in LVEF and exposure was examined. For most patients LVEF was assessed 2-3 times during the study, therefore the lowest LVEF estimate (LVEFmin) was modeled as a function of AUCtot (parent+metabolite). Data was available for 586 patients across tumor types.

The following table shows the models that were fit to the data and the results of the analysis.

Table PM16: Summary of models used in analysis of minimum LVEF vs. total AUC (parent+metabolite).

Number	Model	OBJ	Parameter				
			E0	Slop	POW	Emax	EC50
1 lvefmin_auct_slope03	LVEFmin = E0	3078.538	58.2	-	-	-	-
2 lvefmin_auct_linear3	LVEFmin = E0 • (1 + Slop•AUCT)	3069.659	59.3	-0.0146	-	-	-
3 lvefmin_auct_power3	LVEFmin = E0 • (1 + Slop•$AUCT^{POW}$)	3065.996*	59.9	-0.0426	4.8E-7	-	-
4 lvefmin_auct_emax3	LVEFmin = E0 • (1 + Emin•AUCT/(EC50+AUCT))	3065.996*	59.9	-	-	-0.0426	1.5E-9

where:
Eo: lowest LVEF not due to drug (placebo effect)
AUCT: total AUC (parent+metabolite)
Slop: slope of LVEFmin vs. AUCT relationship
POW: power function value
Emax: maximum change in LVEF
EC50: AUCT corresponding to half-Emax
*: minimization was terminated due to rounding errors

As the table above indicates, including a exposure term in the model (linear model 2) only showed a small reduction in OBJ compared to the intercept model (model 1), suggesting a weak relationship with exposure. The power model estimate of the POW exponent was extremely small, suggest a poor fit. The Emax model showed minimization errors and showed a EC50 estimate that was very small, suggesting a poor fit.
The figures below show the goodness-of-fit plots for the final model, the linear model. Visual inspection of the data also indicated substantial variability in LVEF across exposures, suggesting essentially no consistent relationship with exposure in this dataset.

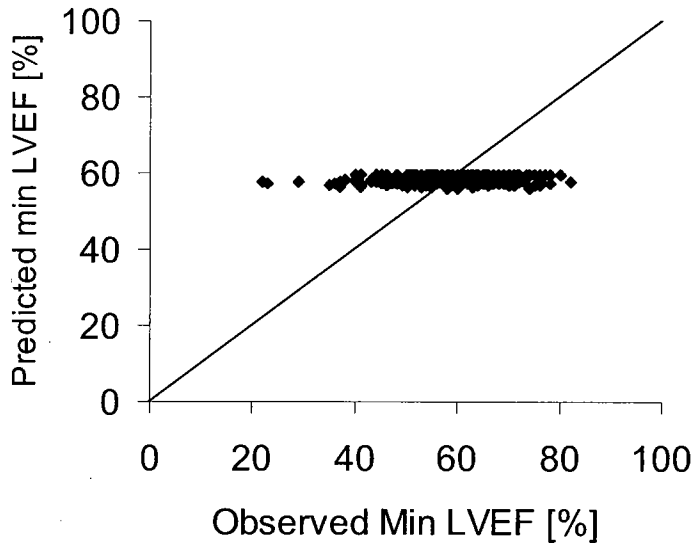

Figure PM50: Observed vs. predicted plot for minimum LVEF. Line represents unity.

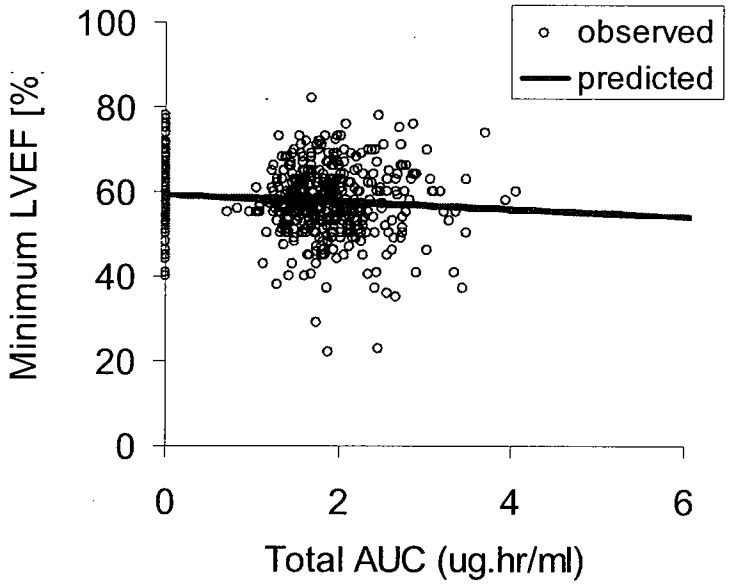

Figure PM51: Minimum LVEF vs. total AUC across patients. Line represents line of best fit. Plot illustrates the substantial variability in response and the modest relationship with exposure.

Question: Are there any differences in these exposure-toxicity relationships between the GIST and MRCC patients?

The influence of tumor type was examined in all of the above analysis, and there were no differences, by tumor type for any of the toxicity measures.

Question: Is there an effect of sex on any of the exposure-toxicity relationships?

If we look at sex differences in the incidence of toxicity, for e.g., fatigue, there appears to be an increased incidence in females – however it is unclear if this is a result of the higher exposures seen in females, and/or if there is a further sex difference in the E-R relationships (or sensitivity).

This can be tested by adding sex as a covariate in the E-R models relating toxicity with AUC. For toxicity measures, adding sex as covariate is not significant, indicating that the observed sex difference in toxicity is probably due to the increased exposure seen in females.

Question: Is there an effect of ECOG performance status on E-R relationships for effectiveness or toxicity?

The influence of ECOG status was examined in all of the above analyses. A dummy variable ISECOG1 was created to categorize those individuals with ECOG scores of 1. There were very few patients with ECOG scores of 2, so it was not evaluated as a separate variable.

Except for grade 3/4 fatigue, ECOG score did not come up as a significant covariate in any of the exposure-toxicity analyses.

As shown above, an ECOG score of 1 was associated with an odds ratio of 2.2 for grade 3/4 fatigue. This means that patients with an ECOG score of 1 had a 2-fold higher probability of showing grade 3/4 fatigue compared to patients who did not have an ECOG score of 1.

III. Population Pharmacokinetic Modeling

Objectives:
The objectives of the population analysis were to describe sunitinib (parent) and SU012662 (primary equipotent metabolite) pharmacokinetics (PK) following single and multiple dose administration of SU011248 in healthy subjects and cancer patients across 13 studies and identify covariates that are important determinants of sunitinib and SU012662 disposition.

The applicant has developed a population model for sunitinib and SU012662, and evaluated a range of covariates for the clearance and volume of distribution. However, their dataset did not include the data from the MRCC studies. Also, their covariate analysis included covariates such as race which included very small numbers of Black and Asian subjects, and ECOG score, which has limited pharmacokinetic significance. This would limit the interpretation of the results. Moreover the effect of tumor type on clearance was not directly evaluated. The Agency approach extends the applicant's analysis by including the 2 MRCC studies and the placebo-controlled GIST study data, and included the evaluation of tumor type as a covariate in the parent and metabolite model.

Sunitinib Pharmacokinetic Summary:
Following oral administration, sunitinib is slowly absorbed from the gastrointestinal tract with maximum concentrations observed from 5 to 16 hours after dosing. Oral bioavailability in humans has not been studied directly, however in primates bioavailability was high (58%) after oral administration. Exposure in humans was similar after oral administration as a freebase, L-malate salt capsules, or when administered with food. Steady-state conditions of sunitinib are reached in approximately 1 to 2 weeks. Plasma protein binding of sunitinib is 95%.
The formation of the N-de-ethyl metabolite of sunitinib to form the pharmacologically active and equipotent SU012662 is primarily mediated by CYP3A4. SU012662 is the primary circulating metabolite formed after administration of sunitinib. Information on the percent of sunitinib converted to SU012662 is not available in humans at the time of this analysis, however in monkeys it is approximately 21%. Peak plasma concentrations of SU012662 were much lower than those of sunitinib and declined more slowly. Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and SU011248 are approximately 40 to 60 hours and 80 to 110 hours, respectively.

Study Design:

Table X1 summarizes the 13 studies that were included in the analysis, and X2 shows the PK sampling schedule for all the studies. Note that the applicant's analysis did not include the last 3 studies listed (014, 1004 and 1006).

Table PM17: Summary of study designs for studies included in population PK analysis. (next page)

Protocol	Design	Type	Population	Sampling	SU011248 Formulation	Dosing	N enrolled
248-ONC-0511-001	Randomized, double-blind, placebo-controlled, single-dose study	SD[1]	Healthy volunteers	Full PK	free base powder in bottle	50 mg Oral Single dose	9
248-ONC-0511-002	Open-label, non-randomized, dose-escalation study	MD[2]	Solid tumor	Full PK and Trough	free base and L-malate salt capsule	25, 50, 75, or 100 mg Oral Repeat doses QD or QOD on Schedule 4/2[3]	28
248-ONC-0511-004	Randomized, open-label, 3-way crossover study of SU011248 free base and L-malate salt and the effect of food,	SD	Healthy volunteers	Full PK	free base and L-malate salt capsule	50 mg, 3 single Oral doses free base fasted L-malate salt fasted, L-malate salt fed	15
RTKC-0511-005	Open-label, non-randomized, dose-escalation study	MD	Solid tumor	Full PK and Trough	free base and L-malate salt capsule	50, 75 QD or QOD Oral Repeat doses on Schedule 4/2 or 2/2[4]	41
248-ONC-0511-006	Open-label, single-treatment, escalating-dose study	SD	AML	Full PK	free base and L-malate salt capsule	Single dose of 50-350 mg	29
RTKC-0511-009	Randomized, open label, 2-way crossover study of SU011248 with and without concomitant administration of Ketoconazole	SD	Healthy volunteers	Full PK	L-malate salt powder in bottle	10 mg + ketoconazole: 400mg po QD x 7 days	27
A6181001	Open-label, crossover study of SU011248 with and without concomitant administration of Rifampin	SD	Healthy volunteers	Full PK	L-malate salt capsule	50 mg + rifampin: 400mg po QD x 7 days	28
RTKC-0511-013	Open-label, single arm, non-randomized, dose-escalating study of 3 treatment schedules	MD	GIST	Trough and Full PK (18 Full PK)	L-malate salt capsule	25, 50, or 75 mg Oral Repeat doses QD on Schedule 2/2, 4/2, or 4/1[5]	97 (18 with full PK)
RTKC-0511-016	Open-label, non-randomized study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50 mg Oral Repeat doses QD on schedule 2/1[6]	12
RTKC-0511-018	Open-label, dose escalation study	MD	Solid tumor	Full PK and Trough	L-malate salt capsule	50-175 mg loading dose on day 1 50 mg Oral Repeat doses QD on schedule 2/1	27
RTKC-0511-014 (Study 014)	open-label, single-arm, multicenter, clinical trial evaluating the efficacy and safety as single-agent, second-line therapy	MD	MRCC	Trough PK	L-malate salt capsule	50 mg Oral Repeat doses QD on schedule 4/2	63
A6181004 (Study 1004)	dual-arm, double-blind, placebo-controlled, multicenter, clinical trial with 2:1 randomization	MD	GIST	Trough PK	L-malate salt capsule	0 or 50 mg Oral Repeat doses QD on schedule 4/2	357
A6181006 (Study 1006)	open-label, single-arm, multicenter, trial evaluating the efficacy and safety as a single-agent	MD	MRCC	Trough PK	L-malate salt capsule	50 mg Oral Repeat doses QD on schedule 4/2	106

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

Table PM18: Pharmacokinetic Sampling Summary[1,2]

Protocol	Type	Scheduled Nominal Full Sampling	
		Study Day	**Time-points**
248-ONC-0511-001	SD	Day 1	Pre-dose (0), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 16, 24, 30, 36 & 48 hrs post-dose
248-ONC-0511-002	MD	Cycle 1: Days 1 & 27 or 28	Pre-dose (0), 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16 & 24 hrs post-dose
248-ONC-0511-004	SD	Day 1	Pre-dose (0), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 16, 24, 30, 36, 48, 72 & 216 hrs post-dose
248-ONC-0511-005	MD	Schedule 2/2 • Cycle 1: Days 1 & 13 or 14 • Cycles 2 & 3: Day 13 or 14 Schedule 4/2 • Cycle 1: Days 1 & Day 28 • Cycles 2 & 3: Day 28	Pre-dose (0), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 20, 24 & 48 hrs post-dose
		Schedule 4/2 Cycle 1: Day 14	Pre-dose (0), 4, 6, 8, 10, 12, & 24 hrs post-dose
248-ONC-0511-006	SD	Day 1	Pre-dose (0), 4, 6, 8, 10, 12, 24 & 48 hrs post-dose
RTKC-0511-009	SD	Day 1	Pre-dose (0), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 30, 36, 48, 72, 120, 168, 216, 312, 408, & 504 hrs post-dose
RTKC-0511-013	MD	Schedule 2/2 • Cycle 1: Days 1 & 14 • Cycle 2: Day 14 Schedule 4/2 • Cycle 1: Days 1 & 28 • Cycle 2: Day 28 Schedule 2/1 • Cycle 1: Days 1 & 14 • Cycle 2: Day 14	Pre-dose (0), 1, 4, 6, 8, 10, 12, 24, & 48 hrs post-dose
RTKC-0511-016	MD	• Cycle 1: Days 1 & 14 • Cycle 2: Day 14 • Cycle 3: Day 14	Pre-dose (0), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 20 & 24 hrs post-dose
RTKC-0511-018	MD	• Cycle 1: Day 1 • Cycle 2: Days 1 & 14 • Cycle 3: Day 14 (for >50 mg)	Pre-dose (0), 4, 6, 8, 10, 12 & 24 hrs post-dose
		Cycle 1: Day 14	Pre-dose (0), 4, 6, 8, 10, 12, 24, 72 & 120 hrs post-dose
A6181001	SD	Day 1	Pre-dose (0), 2, 4, 7, 8, 9, 12, 16, 24, 36, 48, 72, 144, 240, 288, 336 & 408 hrs post-dose
Protocol	**Type**[3]	**Scheduled Nominal Trough Sampling**	
248-ONC-0511-002	MD	Days 4, 7, 10, 13, 19 & 25	
248-ONC-0511-005	MD	Schedule 2/2 • Cycle 1: Days 7 & 29 • Cycles 2 & 3: Days 7, 17, 22, & 29 Schedule 4/2 • Cycle 1: Days 7, 17, 22 & 43 • Cycles 2 & 3: Days 7, 14, 17, 22, 32, 35, 40, & 43	

RTKC-0511-013	MD	Schedule 2/2 • Cycle 2: Day 1 • Cycle 3: Days 1 & 14 Schedule 4/2 • Cycle 1: Day 14 • Cycle 2: Days 1 & 14 • Cycle 3: Days 1, 14 & 28 Schedule 2/1 • Cycle 2: Day 1 • Cycle 3: Days 1 & 14
RTKC-0511-016	MD	• Cycle 1: Day 7 • Cycles 2 & 3: Days 1 & 7
RTKC-0511-018	MD	• Cycle 1: Days 4, 7 & 10 • Cycle 2: Day 7 • Cycle 3: Day 1
RTKC-0511-014 (Study 014)	MD	• Cycle 1: Days 14, & 28 • Cycle 2: Day 28 • Cycle 3: Day 28
A6181004 (Study 1004)	MD	• Cycle 1: Days 14, & 28 • Cycle 2: Day 28 • Cycle 3: Day 28
A6181006 (Study 1006)	MD	• Cycle 1: Days 14, & 28 • Cycle 2: Day 28 • Cycle 3: Day 28

1: Based on clinical study reports, 2: Up to cycle 3, 3: SD: Single Dose, MD: Multiple Dose

Datasets:
The analyzed dataset included parent and metabolite concentrations collected in subjects from 13 clinical studies at timed intervals following both single and multiple dose regimens in healthy volunteers and oncology patients.

The datasets included subject identification, dosing information, time of sample collection, parent molecule and metabolite concentrations, demographic, and physiologic characteristics. Plasma concentrations versus time data were analyzed using nonlinear mixed-effects modeling to estimate parent and metabolite population pharmacokinetic parameters (mean and inter-subject variability) as well as relationships between the pharmacokinetic parameters and weight, race, gender, tumor type, age, ALT, CRCL, and ECOG score.

Software:
All non-linear mixed effects modeling was performed using NONMEM version V.

Methods:
The plasma concentration versus time data of the parent and metabolite could not be modeled simultaneously and were therefore modeled separately. The base model for the parent molecule was a two-compartment oral model. The metabolite molecule was also modeled using a two compartment model.

Base model selection was carried out using first-order estimation. The selected base models were then analyzed for covariate influence on the inter-individual error terms. Full models (including all potential relationships identified from an exploratory investigation) were then built for both the parent and metabolite, using first-order estimation.

To identify significant covariates, a stepwise forward selection method was used. This differs from the applicant's approach, which was to use a backward elimination method. Individual covariates were included one at a time, and the resulting change in the –2 times the maximum log of the likelihood of the data (i.e., change in NONMEM objective function value, ΔOFV) noted. Covariates were identified as significant at the p=0.001 level (represented by a 10.83 unit change in the OFV) for inclusion in the model.

Results:

The plasma concentration versus time data of the parent and metabolite could not be modeled simultaneously and were therefore modeled separately. The parent molecule was modeled using a two-compartment oral model. The following figure shows the observed vs. predicted plot for the parent base model fit.

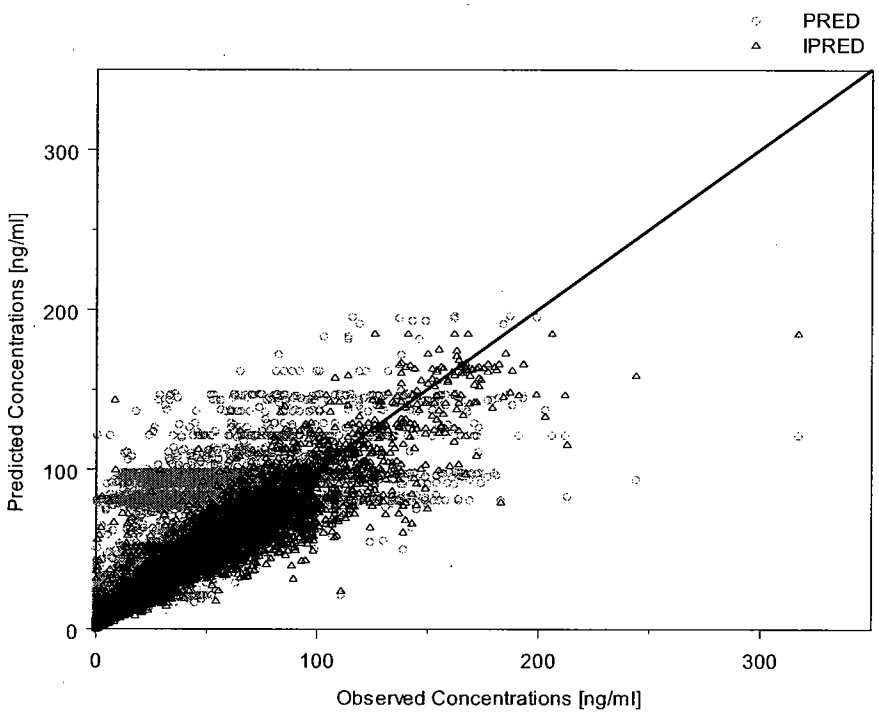

Figure PM52: Observed vs. Predicted concentration (gray symbols: population-predicted and black symbols: individual-predicted) for parent molecule base model. Line represents unity.

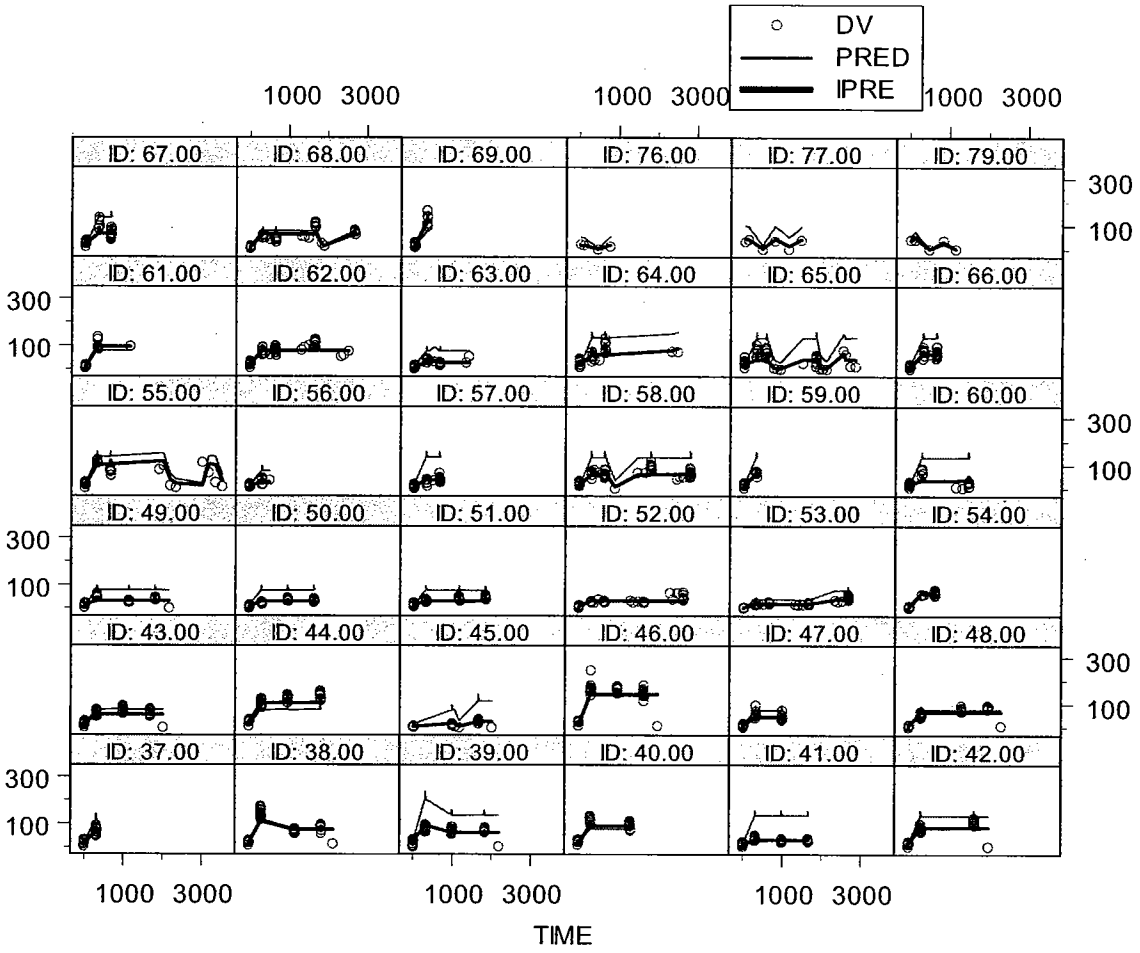

Figure PM53: Sunitinib (parent) concentration vs. time profiles for representative sample of patients. Symbols represent observed data, thin line represents the population predicted and thick line represents the individual predicted concentration vs. time curves.

The following table shows the final parameter estimates for the parent base model.

Appears This Way
On Original

Table PM19: Parent Pharmacokinetic Base Model Parameter Values

Parameter	Value (Standard Error of Estimate %)	%Inter-individual Variability (Standard Error of Estimate %)
CL/F (L/hr)	23 (8.5%)	42.1 (19.9%)
Vd/F central (L)	2140 (5.5%)	35.3 (12.8%)
Ka (1/hr)	0.642 (4.6%)	113.1 (9.8%)
Intercompartmental flow (Q (L/hr))	8.3 (45.5%)	NA
Vd peripheral (L)	46500 (43.4%)	NA
Proportional Error (%CV)	21.6 (7.5%)	NA

The metabolite was also modeled with a 2-compartmenr oral model. The following figure shows the observed vs. predicted concentrations for the metabolite model.

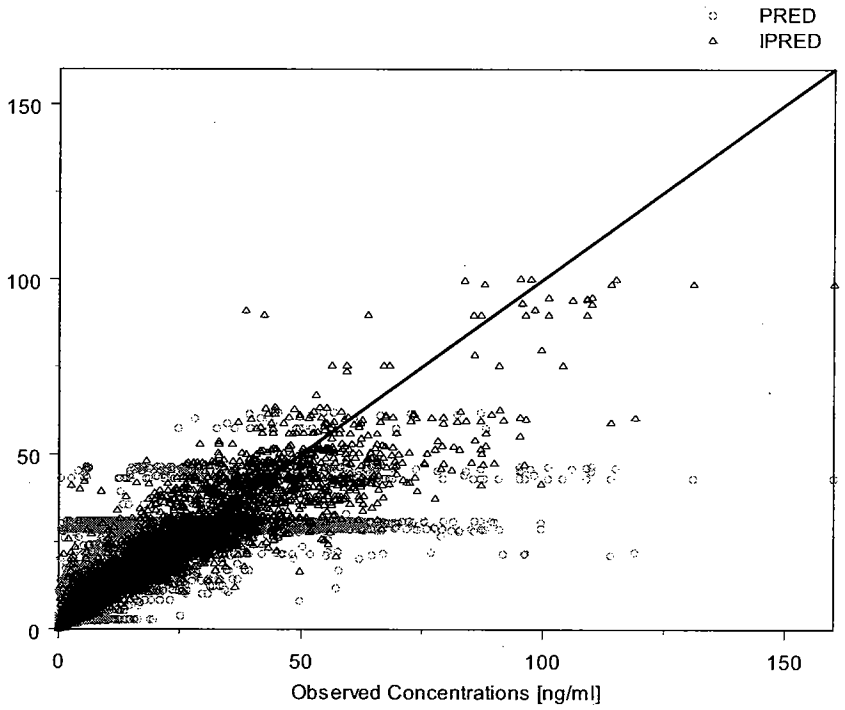

Figure PM54: Observed vs. Predicted concentration (gray symbols: population-predicted and black symbols: individual-predicted) for metabolite base model. Line represents unity.

Table PM20: Metabolite Pharmacokinetic Base Model Parameter Values

Parameter	Value (Standard Error of Estimate)	%Inter-individual Variability (Standard Error of Estimate)
CL/F (L/hr)	14.6	45.7
Vd/F central (L)	3650	118.7
Ka (1/hr)	0.781	145.9
Intercompartmental flow (Q (L/hr))	5.34	NA
Vd peripheral (L)	8.3E+8	NA
Proportional Error (%CV)	29.1	NA

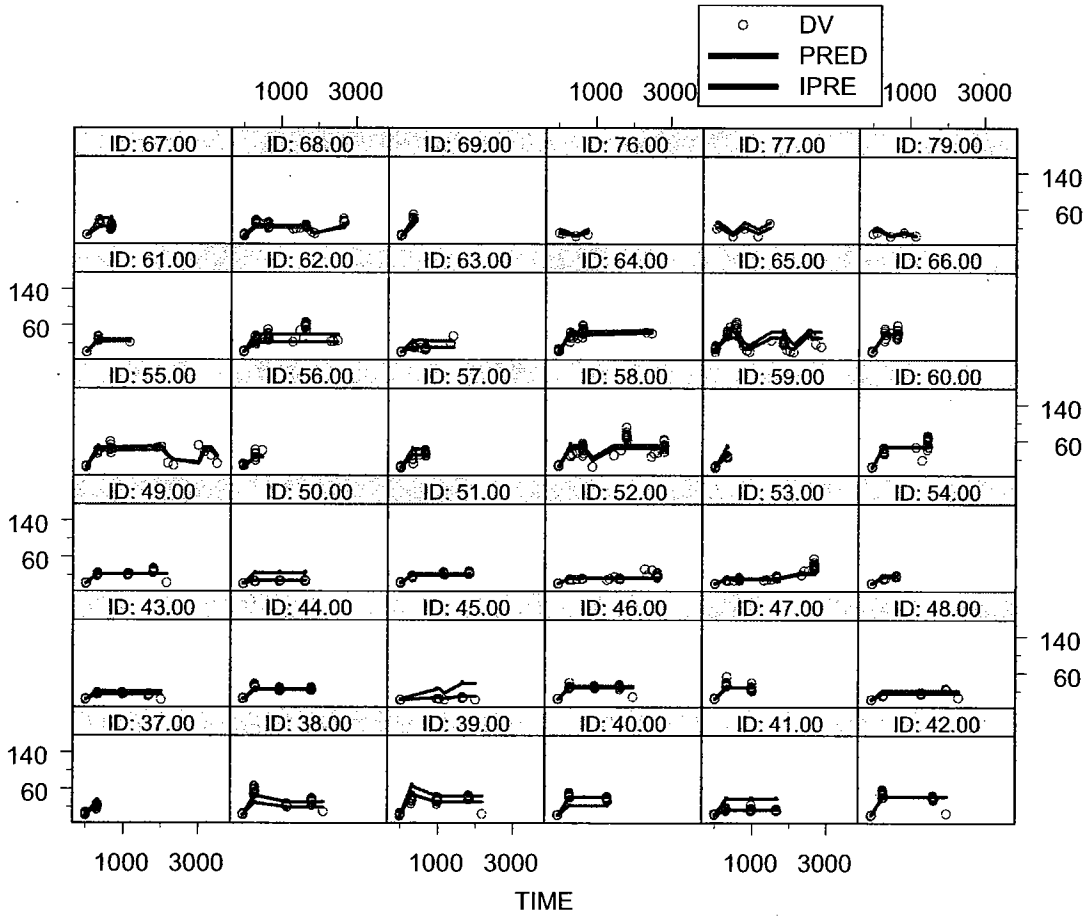

Figure PM54: SU012662 (metabolite) concentration vs. time profiles for representative sample of patients. Symbols represent observed data, thin line represents the population predicted and thick line represents the individual predicted concentration vs. time curves.

Covariate Effects:
The following covariates were evaluated for their effect on the PK of sunitinib and its metabolie SU012662.

CL/F: Gender, Age, Weight, Race, ECOG score, Tumor type, CLcr
Vd/F: Gender, Age, Weight, Race, ECOG score, Tumor Type

Table PM21 includes descriptive statistics of the covariates that were included as continuous variables, and table PM22 includes the counts for each of the covariates included as categorical variables.

Table PM21: Summary values at screening of continuous covariates.

Variable	Age (y)	Weight (kg)
Mean	53.1	78.2
Standard Deviation	14.6	18.8
Median	55.0	77.3
Min	18.0	34.2
Max	87.0	167.5
Total N	596	596

Table PM22: Number of subjects for each categorical covariate.

Covariate	Subgroup	Count
Gender	Males	400
	Females	196
Race	White	519
	Black	16
	Asian	47
	Other	14
ECOG Score	0	299
	1	262
	2	35
Tumor Type	None (Healthy)	73
	Solid tumor	107
	AML	29
	GIST	229
	MRCC	158

Due to the very small number of subjects/patients who were not white, race was not included as a covariate.

Initial screening of covariates was performed by plotting the ETA for CL/F and ETA for Vd/F from the base models of parent and metabolite against the covariates (scatter-plots for continuous and box-plots for categorical covariates) to obtain an initial assessment of the potential relationships. The plots for the variables that appeared to show an effect are shown in the following figures.

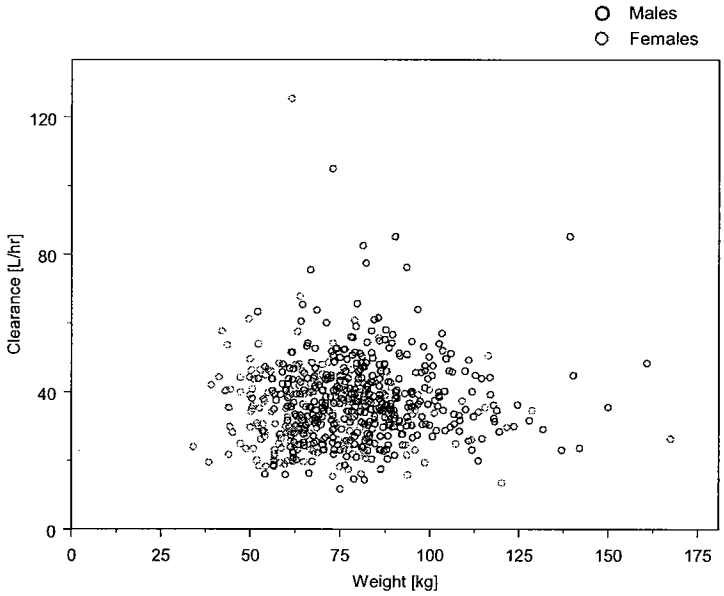

Figure PM55: Scatter plots of ETA-CL/F vs. weight for parent. Data are plotted separately for males and females. The plot indicates the lack of a potential relationship of CL/F with body weight, across gender.

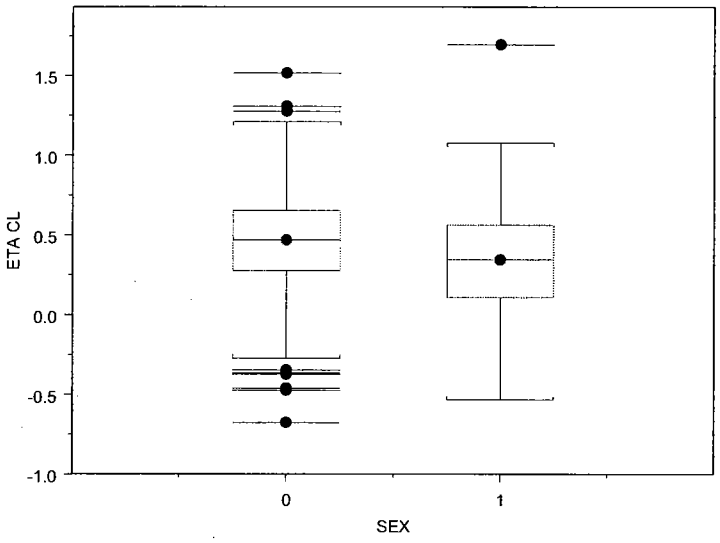

Figure PM56: Box plots of ETA-CL/F vs. sex for parent. Females (sex=1) appear to show lower values compared to males.

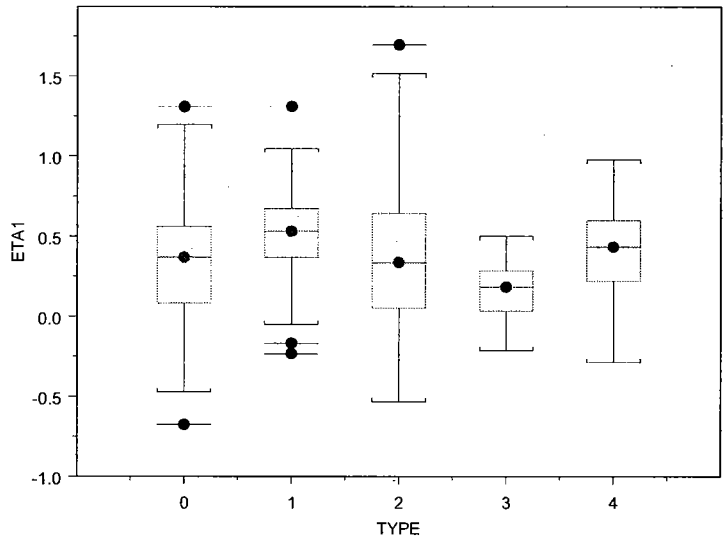

Figure PM57: ETA-CL/F by tumor type for parent. 0: healthy subjects, 1: GIST, 2: solid tumors, 3: AML, 4: MRCC.

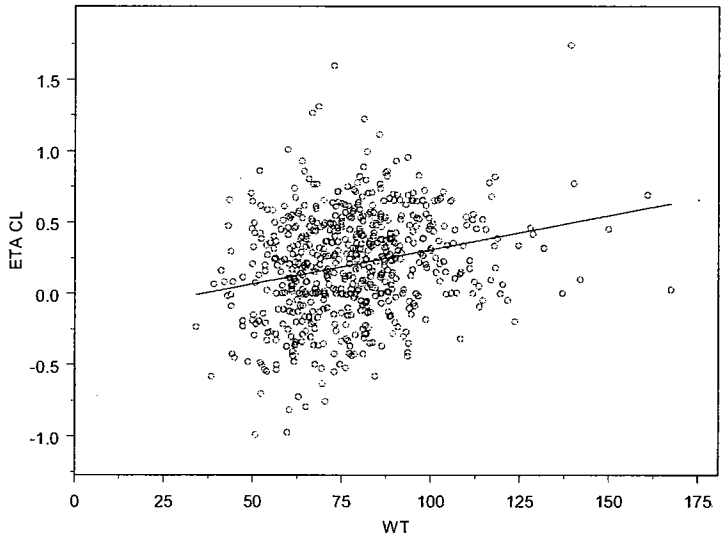

Figure PM58: Scatter plots of ETA-CL/F vs. weight for metabolite, indicating the potential relationship of CL/F with body weight.

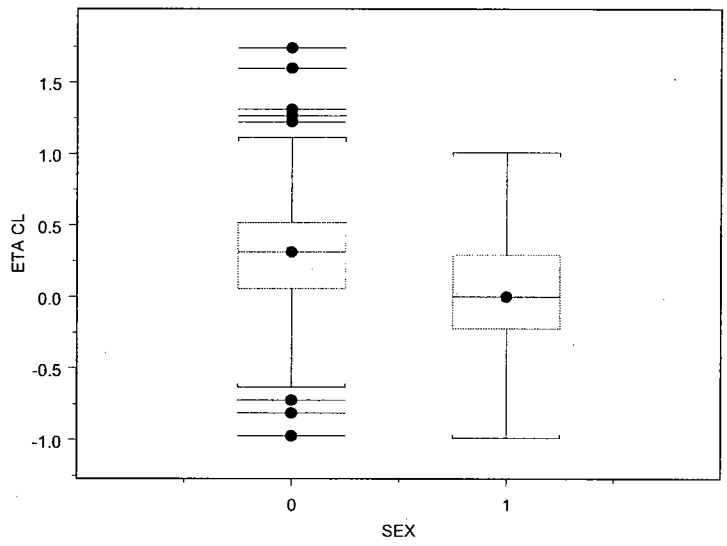

Figure PM59: Box plots of ETA-CL/F vs. sex for metabolite. Females (sex=1) appear to show lower values compared to males.

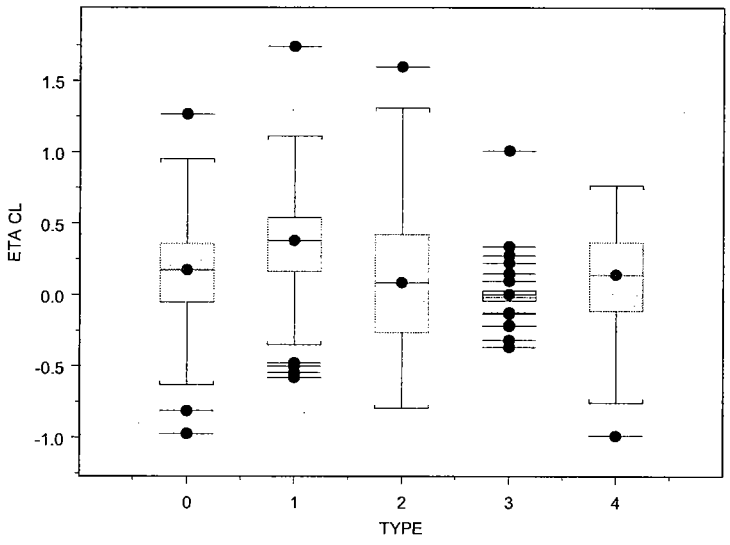

Figure PM60: ETA-CL/F by tumor type for metabolite. 0: healthy subjects, 1: GIST, 2: solid tumors, 3: AML, 4: MRCC.

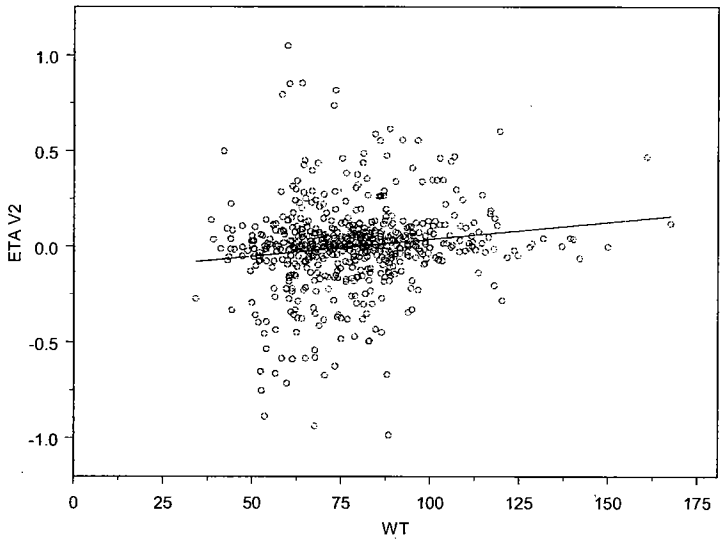

Figure PM61: Scatter plots of ETA-Vd/F vs. weight for parent, indicating the potential relationship of Vd/F with body weight.

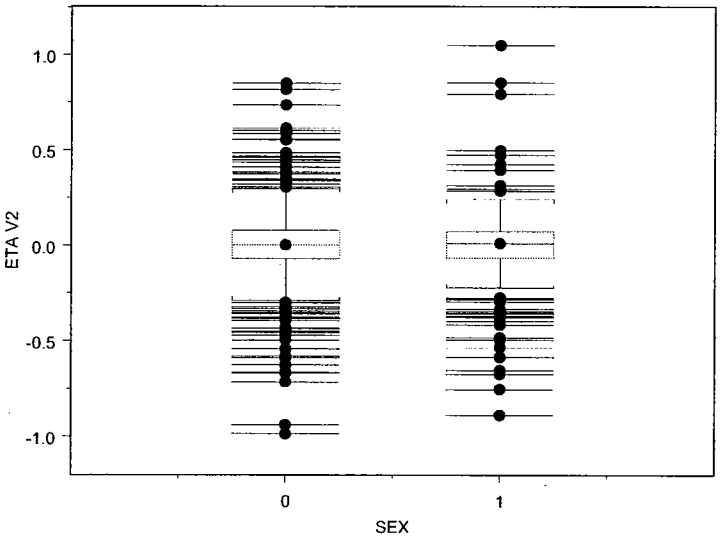

Figure PM62: Box plots of ETA-Vd/F vs. sex for parent.

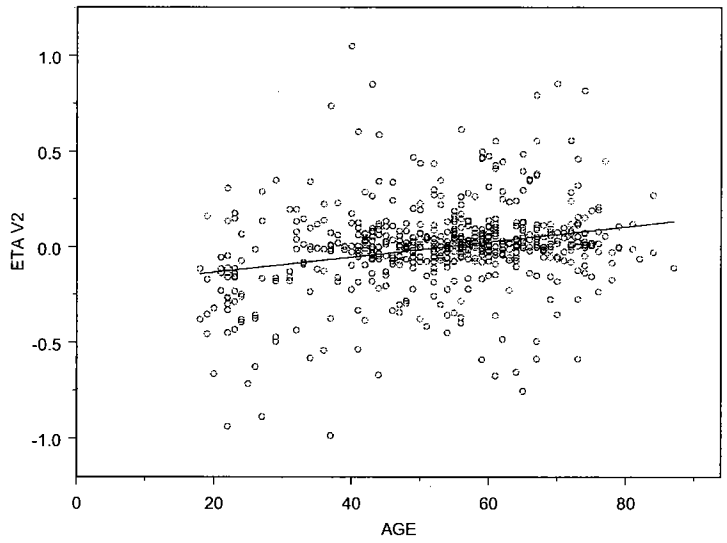

Figure PM63: Scatter-plot of ETA-Vd/F vs. age for parent.

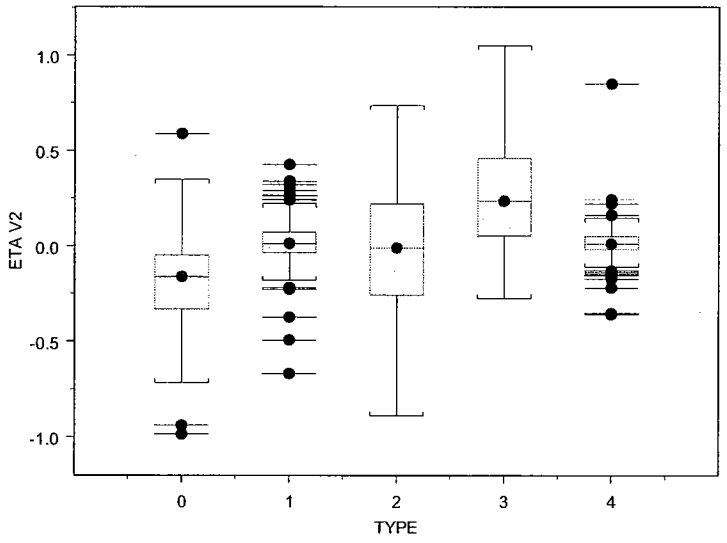

Figure PM64: Box-plot of ETA-Vd/F vs. tumor type for parent.

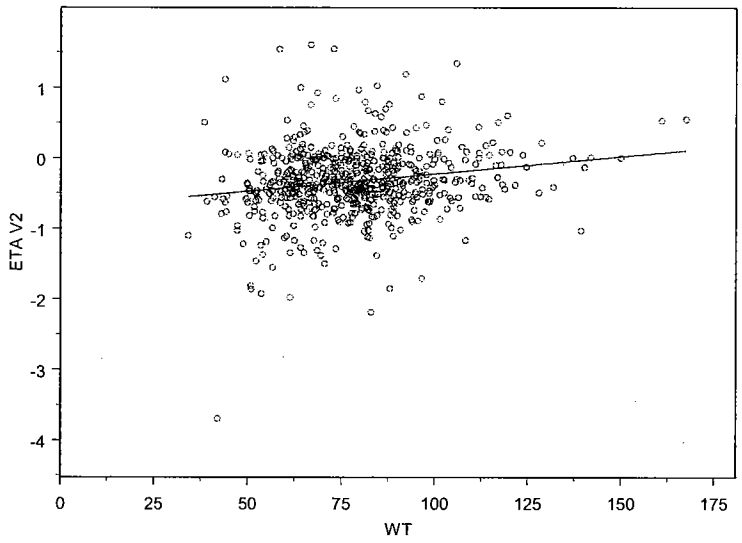

Figure PM65: Scatter-plot of ETA-Vd/F vs. body weight for metabolite.

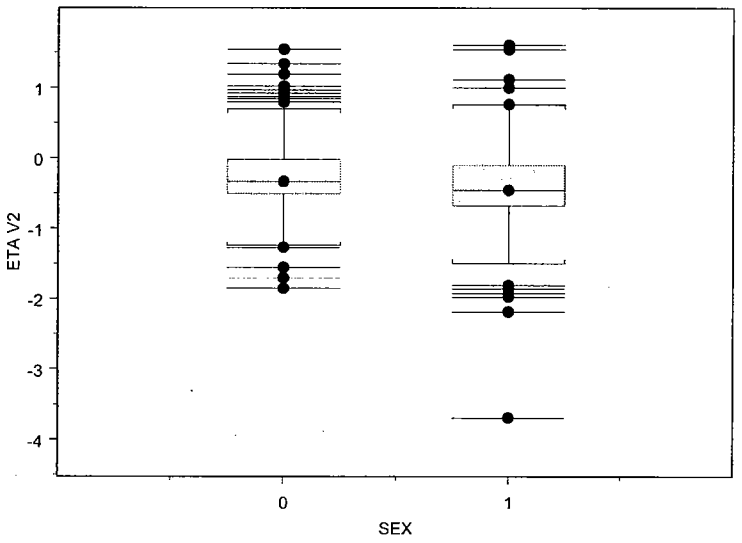

Figure PM66: Box-plot of ETA-VD/F vs. sex for metabolite. Sex=0: males, Sex=1: females.

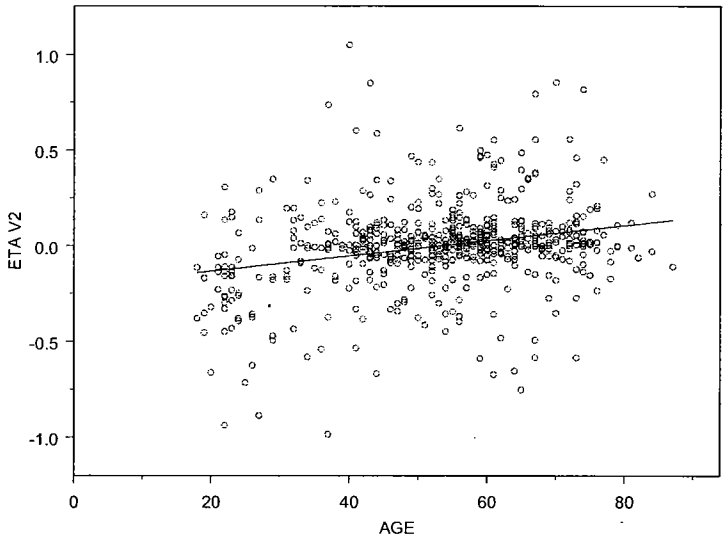

Figure PM67: Scatter-plot of ETA-Vd/F vs. age for metabolite.

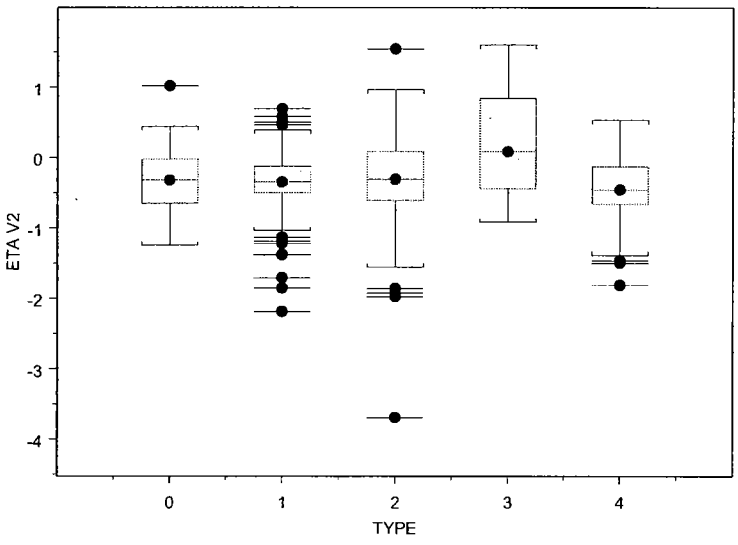

Figure PM68: Box-plot of ETA-Vd/F vs. tumor type for metabolite.

This preliminary screen showed that covariates identified on CL/F of the parent were gender (females relative to males), ECOG score and tumor type. There did not appear to be any relationship between ETA for CL/F and body-weight. Covariates identified on Vd/F were

gender, weight, age, ECOG score, and tumor type (relative to healthy volunteers). From the range of clinical data included, no relationship with renal or hepatic function was observed.

All covariates were added to the base model using forward selection. At the addition of each covariate, the decrease in objective function was observed vs. predicted concentration plots were examined to guide covariate selection as described above.

The following table shows the minimum objective function values for each of the covariate models.

Table PM23: Minimum objective function for covariate models for parent drug.

		Covariates on CL/F				Covariates on Vd/F			
Model	OBJ	Wt	Sex	Age	Tumor Type*	Wt	Sex	Age	Tumor Type*
1 (base)	44289								
2	44282	X							
3	43633		X						
4	43633	X	X						
5	43633		X	X					
6	43529		X			X			
7	43632		X				X		
8	43524		X			X	X		
9	43205		X			X	X	X	
10 (final)	42496		X		X	X	X	X	X

*: thetas for each tumor type added individually.

Table PM24: Minimum objective function for covariate models for metabolite.

		Covariates on CL/F				Covariates on Vd/F			
Model	OBJ	Wt	Sex	Age	Tumor Type*	Wt	Sex	Age	Tumor Type*
1 (base)	26986								
2	26563	X							
3	26167		X						
4	26136	X	X						
5	25945	X	X			X			
6	25869	X	X			X	X		
7	25864	X	X			X	X	X	
8	25071	X	X		X	X	X	X	
9 (final)	24765	X	X		X	X	X	X	X

*: thetas for each tumor type added individually.

Final Model:
Tables PM25 and PM26 show the final parameter estimates for the final models for parent and metabolite.

Table PM25: Parameter Estimates from Parent Final Model

Parameter	Estimate (IIV [d])	CV [e]
CL/F (L/hr)	36.6 (37%)	6.3%
Vd/F central (L)	2440 (87%)	6.4%
Ka (1/hr)	0.65 (132%)	4.3%
Q (L/hr)	6.53	27.0%
Vd/F peripheral (L)	14500	54.8%
Gender on CL/F [a]	-0.351	12.9%
GIST on CL/F [a]	-0.0646	162.5%
Solid tumor on CL/F [a]	-0.204	30.6%
AML on CL/F [a]	0.428	46%
MRCC on CL/F [a]	-0.098	111.6%
Wt on Vd/F [b]	0.394	27.7%
Age on Vd/F [b]	0.114	61.3%
Gender on Vd/F [c]	-0.187	29.7%
GIST on Vd/F [c]	-0.237	47.7%
Solid Tumor on Vd/F [c]	0.135	80%
AML on Vd/F [c]	1.09	25.2%
MRCC on Vd/F [c]	1.58	30.4%
Sigma (proportional error)	0.0408	8%

a: CL/F = θCL/F•(1 + θcovariate•0 or 1): 0 if covariate does not apply to current subject
b: Vd/F = θVd/F• (covariate value/median covariate value)$^{\theta covariate}$
c: Vd/F = θVd/F• (1 + θcovariate• 0 or 1): 0 if covariate does not apply to current subject
d: Inter-individual variability, calculated as (ϖ^2• 100%)
e: Coefficient of variation, calculated as (SEE / estimate • 100%)

Parameter model equations:

$$CL/F = 31.2 \bullet (1 - 0.351 \bullet SEX) \bullet (1 - 0.0646 \bullet GIST) \bullet (1 - 0.204 \bullet ST) \bullet (1 + 0.428 \bullet AML) \bullet (1 - 0.098 \bullet MRCC)$$

$$Vd/F = 2440 \bullet \left(\frac{Wt}{75}\right)^{0.394} \bullet (1 - 0.187 \bullet SEX) \bullet \left(\frac{age}{50}\right)^{0.114} \bullet (1 - 0.187 \bullet GIST) \bullet (1 + 0.135 \bullet ST)$$

$$\bullet (1 + 1.09 \bullet AML) \bullet (1 + 1.58 \bullet MRCC)$$

where SEX=0 for males, 1 for females; GIST=1 for GIST patients, 0 otherwise; ST=1 for solid tumor patients, 0 otherwise; AML=1 for AML patients, 0 otherwise; MRCC=1 for MRCC patients, 0 otherwise.

Table PM26: Parameter Estimates and Confidence Intervals from Metabolite Final Model

Parameter	Estimate (IIV [f])	CV [g]
CL/F (L/hr)	25.1 (38%)	7%
Vd/Fcentral(L)	3830 (72%)	10%
Ka (1/hr)	0.81 (119%)	10%
Q (L/hr)	3.35	21%
Vd/Fperiph(L)	4.3E+8	57%
Weight on CL/F [a]	0.522	30%
Gender on CL/F [c]	-0.379	18%
GIST on CL/F [c]	-0.162	54%
Solid tumor on CL/F [c]	-0.308	22%
AML on CL/F [c]	-0.554	70%
MRCC on CL/F [c]	-0.476	13%
Weight on Vd/F [b]	0.784	33%
Age on Vd/F [b]	0.266	56%
Gender on Vd/F [d]	-0.194	57%
GIST on Vd/F [d]	-0.576	23%
Solid tumor on Vd/F [d]	-0.0683	202%
AML on Vd/F [d]	0.435	48%
MRCC on Vd/F [d]	-0.0636	442%
Sigma (proportional error)	0.0703	9%

a: CL/F = θCL/F• (covariate value/median covariate value) θcovariate
b: Vd/F = θVd/F• (covariate value/median covariate value) θcovariate
c: CL/F = θCL/F• (1 + θcovariate• 0 or 1): 0 if covariate does not apply to current subject
d: Vd/F = θVd/F• (1 + θcovariate• 0 or 1): 0 if covariate does not apply to current subject
e: Apparent bioavailability = 0.21 + θcovariate• 0 or 1: 0 if covariate does not apply to current subject
f: Inter-individual variability, calculated as (ϖ2• 100%)
g: Coefficient of variation, calculated as (SEE / estimate • 100%)

Parameter model equations:

$$CL/F = 25.1 \bullet \left(\frac{Wt}{75}\right)^{0.522} \bullet (1 - 0.379 \bullet SEX) \bullet (1 - 0.162 \bullet GIST) \bullet (1 - 0.308 \bullet ST) \bullet (1 - 0.554 \bullet AML) \bullet (1 - 0.476 \bullet MRCC)$$

$$Vd/F = 3830 \bullet \left(\frac{Wt}{75}\right)^{0.784} \bullet (1 - 0.194 \bullet SEX) \bullet \left(\frac{age}{50}\right)^{0.266} \bullet (1 - 0.576 \bullet GIST) \bullet (1 - 0.0683 \bullet ST)$$

$$\bullet (1 + 0.435 \bullet AML) \bullet (1 - 0.0636 \bullet MRCC)$$

where SEX=0 for males, 1 for females; GIST=1 for GIST patients, 0 otherwise; ST=1 for solid tumor patients, 0 otherwise; AML=1 for AML patients, 0 otherwise; MRCC=1 for MRCC patients, 0 otherwise.

The following figures show the observed vs. predicted plots for the parent and metabolite models.

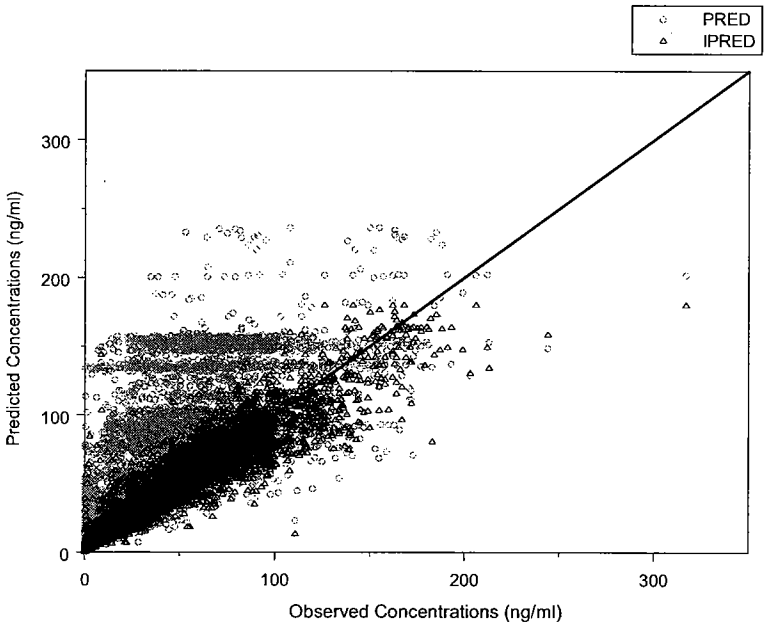

Figure PM69: Observed vs. Predicted concentration (gray symbols: population-predicted and black symbols: individual-predicted) for parent final model. Line represents unity.

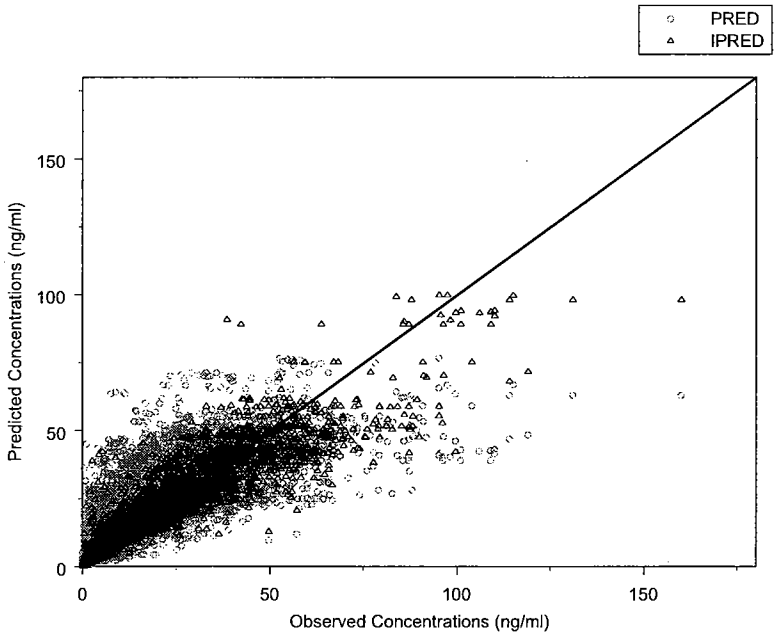

Figure PM70: Observed vs. Predicted concentration (gray symbols: population-predicted and black symbols: individual-predicted) for metabolite final model. Line represents unity.

Summary of findings of the covariate analysis:

- Gender, weight and tumor type described a portion of the variability of the parent and metabolite CL/F.
- Weight, gender, age and tumor type explained some of the variability of Vd/F.
- Relative to males, females displayed a 41% lower CL/F of the parent and a 38% lower CL/F of the metabolite, relative to males. For Vd/F, females displayed a 20% lower value for the parent and a 20% lower value for the metabolite, relative to males.
- Weight was positively correlated with CL/F of the metabolite and Vd/F of both parent and metabolite.
- Age was positively correlated with Vd/F for both the parent and metabolite.
- The effect of race was not evaluated in our analysis due the very small number of Black (n=16) and Asians (n=47) in the dataset (total n=596). Any significant effects would be difficult to interpret and extrapolate from this sample.
- Tumor type did have a significant effect on CL and Vd, although the magnitude of the effect was generally small.
- However, inclusion of all significant covariates did not have an appreciable effect on the inter-individual variability in CL and Vd for the parent or the metabolite. This indicates that these covariates do not improve the predictability of the model, and there are sources of considerable variability that remain unaccounted for.

Conclusions:

- The PK of sunitinib and its primary metabolite SU012662 were described using separate 2-compartment first-order models. The population estimates of the PK parameters were obtained.
- Covariate models were developed to identify important determinants of the clearance and Vd/F for sunitinib and SU012662. The final model indicates significant effects of sex, weight and tumor type on the parent and metabolite CL/F, and age, tumor type, weight and gender on Vd/F.
- Inter-individual variability, after accounting for covariates, was fairly high for the CL/F (40-46%) and Vd/F (36-53%).
- There is a need to continue to collect PK data in ongoing and future studies, along with relevant covariate information, to further refine the model and better describe the sources of variability in the PK of sunitinib and SU012662.

6. OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-938	**Brand Name**	SUTENT
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Sunitinib (SU-011248 L-Malate)
Medical Division	HFD-150	**Drug Class**	Anti-cancer
OCPB Reviewer	Roshni Ramchandani	**Indication(s)**	(1) Treatment of gastrointestinal stromal tumors after failure of imatinib (2) Treatment of metastatic renal cell carcinoma after failure of cytokine-based therapy
OCPB 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	8/10/05	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	12/31/05	**Sponsor**	Pfizer Inc.
PDUFA Due Date	2/11/06	**Priority Classification**	P
Division Due Date	1/11/06		

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	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5		
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	5		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	4		
Transporter studies	X	3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:	X	1		
multiple dose:	X	6		
Dose proportionality -				
fasting / non-fasting single dose:	X			As part of single dose studies in healthy volunteers and patients
fasting / non-fasting multiple dose:	X			As part of multiple dose study in patients
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:				
In-vitro:	X	3		CYP inhibition and induction studies
Subpopulation studies -				
ethnicity:	X			*
gender:	X			*
Pediatrics:				
geriatrics:	X			*
renal impairment:	X			*
hepatic impairment:				

				*: No specific sub-population studies were done. Evaluated as covariates in population PK analysis
PD:				
Phase 2:	X	4		
Phase 3:	X	2		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			Population PK-PD analysis across 6 studies
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			Population PK analysis across 10 studies. Population PK-PD analysis across 6 studies
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	3		Comparison of free base and malate salt formulations (both capsules) Comparison of 50 mg clinical vs. commercial formulation Comparison of 12.5 mg clinical vs. commercial formulation
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	X			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X	1		PPSR previously submitted (06/05)
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What are the PK characteristics of sunitinib in healthy volunteers and patients with solid tumors? What are the effects of various covariates on the PK of sunitinib (pop PK analysis)? What exposure-response relationships were obtained for measures of toxicity and measures of effectiveness in solid tumor patients (pop PK-PD analysis)?	
Other comments or information not included above		
Primary reviewer Signature and Date	Roshni Ramchandani Sophia Abraham	
Secondary reviewer Signature and Date	Brian Booth	

CC: NDA 21-938, HFD-850 (Electronic Entry), HFD-150 (Cottrell), HFD-860 (Mehta, Rahman, Booth, Abraham, Ramchandani), CDR (Biopharm).

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/s/

Roshni Ramchandani
1/13/2006 06:28:17 PM
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Carol Noory
1/17/2006 10:19:46 AM
BIOPHARMACEUTICS

Sophia Abraham
1/17/2006 10:25:16 AM
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1/17/2006 10:49:34 AM
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