Effect of food on the pharmacokinetics of sunitinib malate (SU11248), a multi-targeted receptor tyrosine kinase inhibitor: results from a phase I study in healthy subjects

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The effect of food on the oral bioavailability of sunitinib malate (SU11248, an oral, multi-targeted tyrosine kinase inhibitor with anti-angiogenic and anti-tumor activities) was assessed in a randomized open-label, two-way crossover study. A 50-mg dose of SU11248 was administered to 16 healthy subjects after a 10-h fast in one period and after a high-fat, high-calorie meal in the other period. The 90% confidence intervals (CIs) for maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC) were within the 80–125% bioequivalence range, indicating the absence of a food effect. SU11248 exposure increased slightly in the fed compared with the fasted state (ratios of fed/fasted geometric least square means: C_{max} 104%, AUC_{0-last} and $AUC_{0-\infty}$ both 112%). There was a delay in the formation/absorption of the active metabolite SU12662 in the fed state (mean C_{max} decreased 23%), but exposure remained unaffected (90% CIs for AUC_{0-last} and $AUC_{0-\infty}$were within 80–125%). These results indicate that SU11248 can be administered with or without food. *Anti-Cancer Drugs* 17:353–358 © 2006 Lippincott Williams & Wilkins.

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Introduction

Receptor tyrosine kinases (RTKs) are a group of transmembrane proteins involved in cell-to-cell communication. They are expressed in many cell types, and regulate cell growth, differentiation and angiogenesis. Aberrant activation of RTKs – such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) – have been implicated in triggering the abnormal growth of malignant cells, and promoting the necessary neovasculature required for tumor maintenance and progression [1,2]. In recent years, RTKs have become one of the most important targets in oncology research [3,4].

Sunitinib malate (SU11248) is an oral, multi-targeted RTK inhibitor that specifically inhibits VEG receptors (VEGFR-1, -2 and -3), PDGF receptors (PDGFR-α and -β), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 receptor (FLT3), colony stimulating factor receptor type 1 (CSF-1R) and the glial cell line-derived neurotrophic factor receptor (RET) ([5–8] and Pfizer data on file). SU11248 has demonstrated single-agent anti-tumor activities in phase I and II clinical studies in a variety of advanced solid tumors, including gastrointestinal stromal tumor (GIST), metastatic renal cell carcinoma (mRCC) and metastatic breast cancer [9,10]. The activity observed in early-phase studies involving patients with GIST and mRCC has been confirmed in pivotal studies [11,12].

Orally administered SU11248 is well absorbed in humans, with linear pharmacokinetics at doses of 50–150 mg/day [9]. SU11248 is highly protein-bound and metabolized through *N*-de-ethylation by cytochrome P450 (CYP) 3A4 to SU12662 (Pfizer data on file). SU12662 has a similar inhibitory profile to SU11248 *in vitro* and similar protein binding (Pfizer data on file). SU12662 is further metabolized by CYP3A4 to a minor inactive metabolite (Pfizer data on file).

A randomized, open-label, crossover study (study 248-ONC-0511-004) was conducted to provide an initial assessment of the effect of food on the oral bioavailability of SU11248 in humans (Pfizer data on file). Healthy subjects ($n = 15$) were administered a single 50-mg dose of SU11248 (clinical formulation: L-malate salt capsules) under fasted and fed (780 calories; 30% fat) conditions. Bioequivalence was concluded, since the 90% confidence intervals (CIs) for the comparisons of both maximum plasma concentration (C_{max}) and area under the concentration–time curve from zero to infinity ($AUC_{0-\infty}$) under

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fasted and fed conditions fell within the US Food and Drug Administration (FDA) equivalence limits of 80–125% [13].

The present study (study A6181032) assessed the effect of food on the oral bioavailability of SU11248 using the proposed commercial formulation of SU11248 malate. Subjects received a high-fat, high-calorie meal (approximately 800–1000 calories; 50% fat, 15–20% protein) [13].

Materials and methods

Study design and subjects

This randomized, open-label, two-way crossover study was conducted at a single center in the US (Pfizer Clinical Research Unit, Ann Arbor, Michigan, USA) in accordance with FDA regulations and in compliance with the ethical principles originating in or derived from the Declaration of Helsinki. In addition, the study conformed to the International Congress of Harmonization Good Clinical Practice guidelines. An Institutional Review Board (Pfizer Research Clinic Institutional Review Board, Ann Arbor, Michigan, USA) approved the final study protocol and informed consent was obtained from each subject before the initiation of any study procedures.

Healthy male and female subjects aged between 18 and 60 years were enrolled ['healthy' was defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, clinical laboratory tests and 12-lead electrocardiogram (ECG)]. Pregnant or nursing women and women of childbearing potential not using an acceptable method of non-hormonal contraception were excluded.

Participating subjects had to adhere to certain restrictions, such as abstaining from: all food and drink (except water) for at least 4 h before any safety laboratory evaluation and 8 h before the start of pharmacokinetic sample collection; strenuous exercise for 48 h before blood collection for clinical laboratory tests; alcohol-, caffeine- (including chocolate) and xanthine-containing products from 48 h before receiving SU11248 until collection of the final pharmacokinetic sample in each treatment period; and grapefruit-containing products from 4 days prior to the first dose of SU11248 until collection of the final pharmacokinetic sample. In addition, daily caloric intake was not to exceed approximately 3200 calories and the use of tobacco or nicotine was not permitted throughout the study period. There were also restrictions on concomitant medications: treatment with an investigational drug within 30 days prior to the first dose of SU11248 was not permitted; use of prescription or non-prescription drugs (other than acetaminophen used sporadically and 1 g/day or less), vitamins and dietary supplements within 14 days prior to the first dose of study medication was not permitted; and herbal supplements, hormonal methods of contraception and hormone-replacement therapy had to be discontinued 28 days before the first dose of study medication. These restrictions remained in place for the duration of the study.

Treatments

Subjects were randomized to one of two treatment sequences each comprising two treatment periods (fasted and fed) as shown in Fig. 1. For the fasted period, a single oral dose of SU11248 50 mg was administered after a 10 h fast. For the fed period, a single oral dose of SU11248 50 mg was administered within 30 min of a high-fat, high-calorie meal (two eggs fried in butter, two strips of bacon, two slices of toast with two pats of butter, 4 oz of hash brown potatoes and 240 ml of whole milk). A washout period of at least 4 weeks separated SU11248 dosing between the two treatment periods.

SU11248 was supplied as the proposed commercial formulation (capsules containing L–malate salt equivalent to 50 mg of free base).

Sample collection

Blood samples (4 ml) for pharmacokinetic analysis were collected (into tubes containing EDTA) pre-dose and at the following hours post-dose: 1, 2, 4, 8, 12, 16 and 24 (i.e. day 1), 36 and 48 (day 2), 72 (day 3), 96 (day 4), 120 (day 5), 144 (day 6), 168 (day 7), 192 (day 8), 240 (day 10), 288 (day 12), 360 (day 15), 408 (day 17), 432 (day 18), 456 (day 19), and 480 (day 20). Blood samples were centrifuged (3500 r.p.m., 4°C, 10 min) immediately to separate the plasma, which was stored at –20°C or below until analysis.

Analytical methods

Plasma concentrations of SU11248 and SU12662 were determined by a validated liquid chromatographic tandem mass spectrometric method at Bioanalytical Systems (West Lafayette, Indiana, USA). Briefly, SU11248, SU12662 and a deuterated internal standard of SU11248 were extracted from the plasma organic extraction. SU11248 and SU12662 were detected by positive Turbo-Ionspray ionization in multiple reaction monitoring mode. The lower limit of quantification (LLOQ) for both SU11248 and SU12662 was 0.1 ng/ml. Assay accuracy expressed as bias (%) of quality control (QC) samples ranged from –1.3 to 1.3% and from –1.7 to 2.3% for SU11248 and SU12662, respectively. Assay reproducibility expressed as coefficient of variation (CV%) of QC samples ranged from 2.4 to 6.5% and from 3.7 to 11.1% for SU11248 and SU12662, respectively.

Pharmacokinetics

Plasma pharmacokinetic parameters for SU11248 and SU12662 were calculated by non-compartmental analysis

of concentration–time data using WinNonlin (version 3.2) software. The following pharmacokinetic parameters were calculated: C_{max}, time to reach C_{max} (t_{max}), AUC from time zero to time of the last detectable concentration (AUC_{0-last}), $AUC_{0-\infty}$, terminal half-life ($t_{1/2}$) and apparent oral clearance (CL/F).

C_{max} and t_{max} were determined directly from the plasma concentration data. AUC_{0-last} was calculated using the linear trapezoidal rule. $AUC_{0-\infty}$ was determined using the linear trapezoidal rule from time zero to time of the last detectable concentration, then by extrapolation to infinity using the terminal elimination rate constant (λ_z, which was calculated by log-linear regression of the terminal portion of the plasma concentration–time curve). $t_{1/2}$ was calculated as $0.693/\lambda_z$. CL/F was calculated (for SU11248 only) as dose/$AUC_{0-\infty}$.

Statistical analysis of pharmacokinetic parameters

With a sample size of six subjects in each treatment sequence (i.e. a total of 12 evaluable subjects), this study was designed to have 90% power to ensure the 90% CIs for the ratio of fed/fasted $AUC_{0-\infty}$, AUC_{0-last} and C_{max} fell within 80–125% when there was no difference between the fed and fasted states. This assumed that the expected ratio of the means was 1.00, the intra-subject SD difference on the natural-log scale was 0.20 (based on previous study data) and the differences in means were analyzed by the natural-log transformation of the data. It was planned to enroll a total of 16 subjects to ensure at least 12 evaluable subjects.

The primary parameters for the food-effect analysis were SU11248 C_{max}, AUC_{0-last} and $AUC_{0-\infty}$. A linear mixed-effect statistical model (which included factors accounting for the following sources of variation: sequence; subject nested in sequence, period and treatment) was fitted to each log-transformed parameter. The differences in the means of each log-transformed parameter (fed minus fasted) and 90% CIs for these differences were calculated and then back-transformed to obtain the ratios of the geometric least-squares means (glsmeans) and corresponding 90% CIs. The absence of a food effect was inferred if the 90% CIs for the ratios of the primary parameters were within 80–125%. A similar model was used to analyze the secondary pharmacokinetic parameters. Subjects who had pharmacokinetic parameters for at least one treatment period were included in the statistical comparisons.

Safety assessments

Adverse events (AEs) were recorded throughout the study until 28 days after the last dose of study medication. AEs were graded according to National Cancer Institute Common Terminology Criteria (version 3.0) and causality to study drug was determined by the investigator. Other safety evaluations included physical examinations, clinical laboratory tests, vital signs and ECG measurements.

Results

Subject disposition

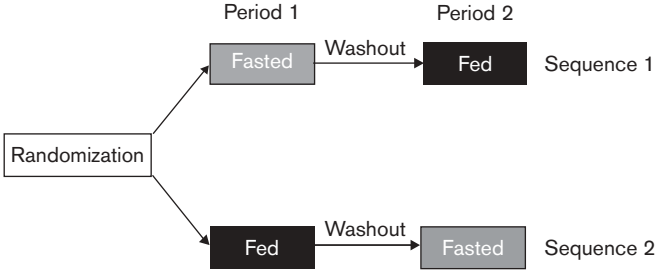
Sixteen healthy subjects were randomized: four men and four women in Sequence 1; six men and two women in Sequence 2. The mean (range) age and weight of the subjects were 45.4 (22–57) years and 80.5 (56.1–95.7) kg, respectively.

Sixteen subjects received a single dose of SU11248 50 mg under fasting conditions and 14 subjects received a single dose of SU11248 50 mg under fed conditions; two subjects (both males randomized to Sequence 1) discontinued prematurely due to AEs (grade 1 and 2 rash). All 16 subjects were included in the pharmacokinetic and safety populations.

Pharmacokinetic results

SU11248 plasma concentrations were measurable 1–2 h post-dose in most subjects and remained above the

Fig. 1

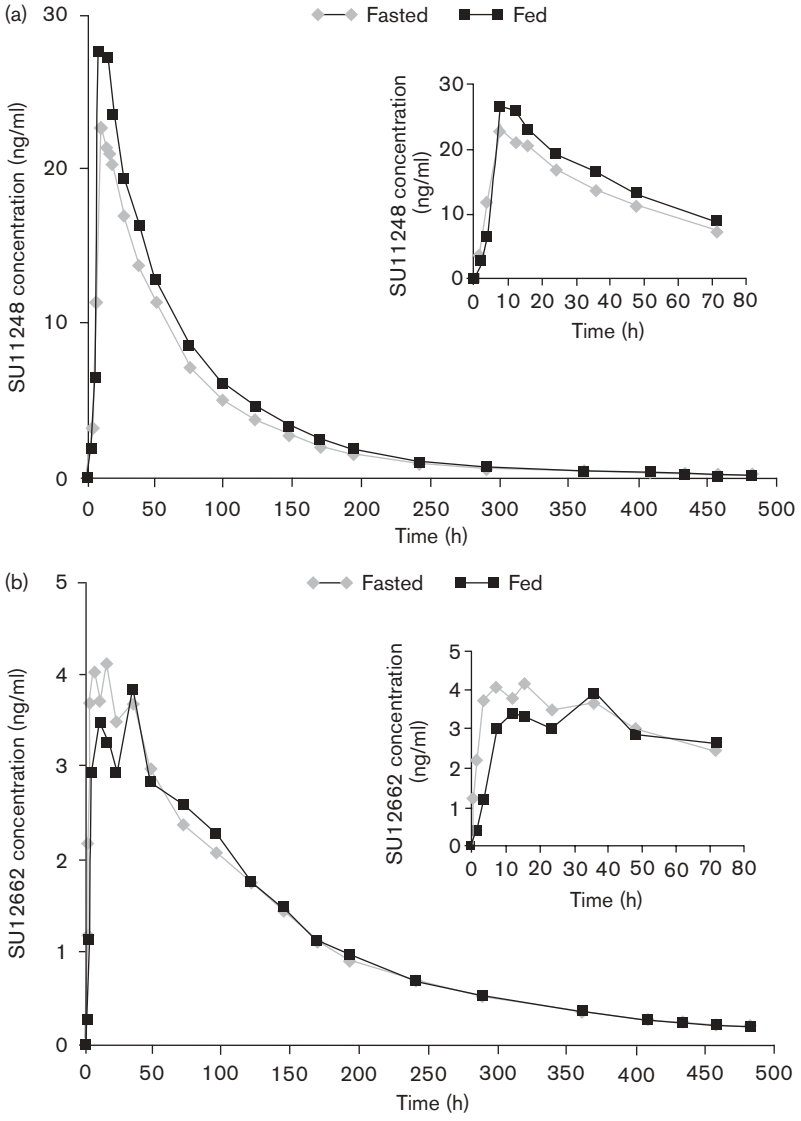


Fasted = a single oral dose of SU11248 50 mg following a 10-h fast

Fed = a single oral dose of SU11248 50 mg following a high-fat, high-calorie meal

Study design.

Fig. 2



SU11248 (a) and SU12662 (b) median plasma concentrations versus time for subjects receiving SU11248 50 mg with and without food.

LLOQ until 288–480 h post-dose (Fig. 2a). SU12662 (the active metabolite) plasma concentrations were measurable 1–2 h post-dose and remained above the LLOQ until 360–480 h post-dose (Fig. 2b).

SU11248 median t_{max} was approximately 8 h post-dose under both fasted and fed conditions (Table 1). SU12662 t_{max} ranged between 4 and approximately 36 h post-dose. Multiple peaks in SU12662 concentrations were observed in many subjects, resulting in variable t_{max} estimates regardless of treatment (i.e. fasted or fed). For both SU11248 and SU12662, there was a bi-exponential decline in plasma concentration (Fig. 2).

Administration of SU11248 with food did not affect SU11248 bioavailability. SU11248 exposure increased slightly in the fed state compared with the fasted state (ratios of fed/fasted glsmeans: C_{max} 104%, AUC_{0-last} and $AUC_{0-\infty}$ both 112%), but the 90% CIs for these parameters were within the bioequivalence range of 80–125% (Table 1).

Administration of SU11248 with food caused a delay in the formation and/or absorption of the metabolite SU12662, resulting in a 23% decrease in SU12662 mean C_{max} (Table 1). While the 90% CIs for SU12662 C_{max} were outside the 80–125% range, those for AUC_{0-last} and

Table 1 SU11248 and SU12662 pharmacokinetic parameters (range) for subjects receiving SU11248 50 mg with and without food

	C_{max} (ng/ml)	AUC_{0-last} (ng·h/ml)	$AUC_{0-\infty}$ (ng·h/ml)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (l/h)
SU11248						
fasted[a] ($n=16$)	25.1 (21.1–29.7)	1476 (1264–1724)	1489 (1276–1736)	8.03 (8.0–16.0)	59.1 (53.4–65.3)	33.6 (28.8–39.2)
fed[a] ($n=14$)	27.6 (23.8–32.0)	1751 (1494–2053)	1765 (1506–2069)	8.0 (8.0–12.0)	61.4 (56.2–67.1)	28.3 (24.2–33.2)
treatment ratio[b]	104 (97–111)	112 (108–116)	112 (108–116)	0.02 (−1.99–2.02)	103 (96–110)	90 (86–93)
SU12662						
fasted[a] ($n=16$)	4.46 (3.5–5.7)	573 (487–675)	606 (518–708)	12.0 (4.0–36.0)	104 (91.7–117)	NA
fed[a] ($n=14$)	3.53 (2.9–4.3)	544 (453–654)	575 (480–688)	36.0 (8.0–36.3)	106 (94.0–120)	NA
treatment ratio[b]	77 (69–86)	92 (89–96)	92 (89–96)	2.00 (−13.9–18.2)	103 (100–107)	NA

NA = not applicable (parameter not calculated for SU12662).
[a]Geometric mean values (95% CIs) presented; except for t_{max}, where medians (ranges) presented.
[b]Ratios (%) of fed/fasted glsmeans (90% CIs) presented; except for t_{max}, where medians (range) presented.

Table 2 Summary of the most common AEs by treatment[a]

Preferred term [*n* (%)]	Fasted ($n=16$)	Fed ($n=14$)	Total ($n=16$)
Headache	5 (31.3)	6 (42.9)	9 (56.3)
Pruritus	5 (31.3)	2 (14.3)	6 (37.5)
Upper respiratory tract infection (not otherwise specified)	1 (6.3)	3 (21.4)	4 (25.0)
Back pain	3 (18.8)	1 (7.1)	4 (25.0)
Dyspepsia	2 (12.5)	2 (14.3)	3 (18.8)
Rash (not otherwise specified)	2 (12.5)	1 (7.1)	3 (18.8)
Somnolence	0 (0.0)	2 (14.3)	2 (12.5)
Cough	2 (12.5)	0 (0.0)	2 (12.5)
Pharyngitis	2 (12.5)	0 (0.0)	2 (12.5)
Vaginal fungal infection (not otherwise specified)	1 (6.3)	1 (7.1)	2 (12.5)

[a]Events occurring in more than one subject in either treatment (i.e. fed or fasted) group; number (%) of subjects reported.

$AUC_{0-\infty}$ were within the bioequivalence range, indicating that the level of SU12662 exposure remained unaffected.

Only a negligible difference in SU11248 t_{max} was observed between the fed and fasted treatment periods; SU12662 t_{max} was prolonged by 2 h (median difference) in the fed compared with the fasted state (Table 1). SU11248 and SU12662 half-lives, and oral clearance of SU11248, were not affected by food (Table 1).

Safety results

The number and percentage of subjects experiencing AEs was 12 (85.7%) and 11 subjects (68.8%) in the fed and fasted states, respectively (Table 2). All AEs were CTC grade 1 or 2 and all resolved [except one unrelated event of grade 1 muscle (eye) twitching]. Two subjects in Sequence 1 discontinued after one treatment period (fasted in both cases) due to grade 1 and 2 rash. No subject experienced a serious AE.

The results of the other safety assessments [physical examinations, clinical laboratory tests, vital signs and ECG measurements (including QTc interval assessment)] did not indicate any unexpected risks of SU11248 treatment under either fed or fasted conditions.

Discussion

Results from this study demonstrate that a high-fat, high-calorie meal did not affect the bioavailability of SU11248. The 90% CIs for the glsmean ratios (fed/fasted) for the primary pharmacokinetic parameters (SU11248 C_{max}, AUC_{0-last} and $AUC_{0-\infty}$) fell within the 80–125% bioequivalence range. Furthermore, SU11248 t_{max} was not affected by the presence of food.

The rate of formation and/or absorption of the active metabolite was decreased by food (a decrease of 23% was observed in mean C_{max}, along with a 2-h prolongation of median t_{max}), but the level of exposure remained unaffected (90% CIs for the glsmean ratios for AUC_{0-last} and $AUC_{0-\infty}$ were within the 80–125% range). Although SU12662 has systemic activity, the decrease in C_{max} is likely to have minimal clinical relevance as SU12662 comprises 25–40% of total drug (SU11248 + SU12662) concentration [14]. SU12662 t_{max} estimates were variable due to multiple peaks in SU12662 plasma concentrations in many subjects. Previous single-dose studies have shown that this occurrence alone (i.e. in the absence of other factors influencing the formation and/or absorption of the metabolite) does not result in variable bioavailability (Pfizer data on file). Preclinical data suggest that SU11248 does not undergo enterohepatic recirculation (Pfizer data on file).

In this study, extensive and prolonged plasma sampling (up to 480 h post-dose) allowed accurate estimation of SU11248 and SU12662 half-lives, which were approximately 60 and 105 h, respectively.

Findings from the safety assessments were similar whether subjects received SU11248 under fed or fasted

conditions. A single 50-mg dose of SU11248 resulted in an acceptable safety profile as the majority of AEs were grade 1–2 in severity and resolved readily.

In conclusion, the bioavailability of the proposed commercial formulation of SU11248 was not affected by consumption of a high-fat, high-calorie meal prior to dosing. The level of exposure (AUC_{0-last} and $AUC_{0-\infty}$) for the primary active metabolite SU12662 remained unaffected. These results indicate that SU11248 can be administered with or without food.

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References

1 Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005; **23**:1011–1027.
2 Ostman A. PDGF receptors – mediators of autocrine tumor growth and regulators of tumor vasculature and stroma. *Cytokine Growth Factor Rev* 2004; **15**:275–286.
3 Melnikova I, Golden J. Targeting protein kinases. *Nat Rev Drug Discov* 2004; **13**:993–994.
4 Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005; **307**:58–62.
5 Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. *Mol Cancer Ther* 2003; **2**:471–478.
6 Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, *et al. In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; **9**:327–337.
7 O'Farrell AM, Foran JM, Fiedler W, Serve H, Paquette RL, Cooper MA, *et al.* An innovative phase I clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. *Clin Cancer Res* 2003; **9**:5465–5476.
8 O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, *et al.* SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity *in vitro* and *in vivo*. *Blood* 2003; **101**:3597–3605.
9 Sakamoto KM. SU-11248 Sugen. *Curr Opin Invest Drugs* 2004; **5**:1329–1339.
10 Miller KD, Burstein HJ, Elias AD, Rugo HS, Cobleigh MA, Pegram MD, *et al.* Phase II study of SU11248, a multitargeted receptor tyrosine kinase inhibitor (TKI), in patients (pts) with previously treated metastatic breast cancer (MBC) [abstract]. *Proc Am Soc Clin Oncol* 2005; **23**:19.
11 Demetri GD, van Oosterom AT, Blackstein M, Garrett C, Shah M, Heinrich M, *et al.* Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of SU11248 in patients (pts) following failure of imatinib for metastatic GIST [abstract]. *Proc Am Soc Clin Oncol* 2005; **23**:308.
12 Motzer RJ, Rini BI, Michaelson MD, Redman BG, Hudes GR, Wilding G, *et al.* Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC)[abstract]. *Proc Am Soc Clin Oncol* 2005; **23**:380.
13 US Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for industry. Food-effect bioavailability and fed bioequivalence studies. Rockville: US FDA; 2002. http://www.fda.gov/cder/guidance/index.htm. [Accessed December 2002].
14 Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N *et al.* Safety, pharmacokinetic, and first evidence of antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol* 2005 [Epub ahead of print].