

Electrocardiographic Characterization of the QTc Interval in Patients with Advanced Solid Tumors: Pharmacokinetic-Pharmacodynamic Evaluation of Sunitinib

Carlo L. Bello,¹ Marilyn Mulay,² Xin Huang,³ Shem Patyna,³ Melissa Dinolfo,² Steven Levine,⁴ Andrew Van Vugt,² Melvin Toh,³ Charles Baum,³ and Lee Rosen²

Abstract Purpose: To evaluate the effects of sunitinib, a multitargeted tyrosine kinase inhibitor, on the QT interval in patients with cancer.

Experimental Design: Patients received sunitinib loading doses (150-200 mg) on days 3 and 9 and maintenance doses (50 mg/d) on days 4 to 8. Moxifloxacin (day 1), placebo (day 2), and granisetron [with placebo (day 2) or sunitinib (days 3 and 9)] were also administered. Treatment effects were evaluated by time-matched, serial electrocardiograms, and manually overread.

Results: Twenty-four of 48 patients were QT/PK evaluable. Moxifloxacin produced a time-matched, maximum mean placebo-adjusted corrected QT interval (QT_cF) of 5.6 ms [90% confidence interval (CI), 1.9-9.3]. Sunitinib QT_cF changes correlated with exposure, but not T_{max}. Maximum mean time-matched, placebo-adjusted QT_cF was 9.6 ms (90% CI, 4.1-15.1) at steady state/therapeutic concentrations (day 3) and 15.4 ms (90% CI, 8.4-22.4) at supratherapeutic concentrations (day 9). No patient had a QT_cF >500 ms. Concomitant granisetron produced no significant QT_cF prolongation. Sunitinib-related adverse events were as previously described.

Conclusions: Sunitinib has a dose-dependent effect on QT interval. The increased risk of ventricular arrhythmias must be weighed against the therapeutic benefit sunitinib provides to patients with advanced cancer. (Clin Cancer Res 2009;15(22):7045-52)

The QT interval represents the duration of ventricular depolarization and repolarization, and is measured with an electrocardiogram (ECG) at the beginning of the QRS interval to the end of the T wave. Key factors affecting QT interval include heart rate, autonomic tone, age, gender, time of day, electrolyte disturbances, and food. Certain pharmacologic therapeutic agents also delay cardiac repolarization and prolong QT interval; these effects are exacerbated by drug-drug interactions (1). These

agents therefore increase the risk of cardiac arrhythmias, including torsade de pointes, which can degenerate into ventricular fibrillation, leading to sudden death. Consequently, evaluation of potential cardiac effects, including those on the cardiac conduction system, is a consideration in designing appropriate clinical trials to assess an agent's risk to patients, assess a compound's overall safety, and provide guidance for the clinical management of any effect.

According to International Conference on Harmonization E14 guidance, all drugs must undergo a formal clinical evaluation early in clinical development to assess the potential for QT/QT_c prolongation (2). Typically, a single dedicated trial (a thorough QT/QT_c trial; TQT) is included in the drug development program and is conducted in healthy volunteers at doses higher than those clinically administered (e.g., "worst case scenario") to characterize dose-response. A TQT should also be randomized and blinded. The use of a placebo control, as well as a concurrent positive control group, is important to rule out non-drug effects and to establish the sensitivity of the trial to detect a known QT interval effect. However, anticancer drugs present a challenge for a TQT trial. These agents are often difficult to administer to healthy volunteers especially at supratherapeutic concentrations. It may be necessary to conduct a trial in cancer patients with a modified design to achieve TQT objectives.

Sunitinib malate (Sutent) is an orally active, multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), platelet-derived

Authors' Affiliations: ¹Pfizer Global Research and Development, New York, New York, ²Premiere Oncology, Santa Monica, California, ³Pfizer Global Research and Development, La Jolla, California, and ⁴St. John's Hospital, Santa Monica, California

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Requests for reprints: Carlo Bello, Pfizer Global Research and Development, 219 E 42nd St, New York, NY 10017. Phone: 212-733-7391; Fax: 646-441-4314; E-mail: Carlo.bello@pfizer.com.

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Translational Relevance

Drug-induced torsade de pointes is a major concern for new drugs seeking regulatory approval. A wide variety of pharmaceutical agents have been implicated as torsadogens, including anticancer agents. Recent International Conference on Harmonization guidelines (ICH E14) provide guidance and recommendations for the clinical evaluation of drugs in development. However, there are many challenges related to the methodology of measurements of drug-induced effects on cardiac repolarization and multiple factors such as coadministration of drugs, electrolyte imbalances, and heredity (e.g., long QT syndrome) that might increase an individual patient's risk of the development of a dangerous arrhythmia. This study was conducted in advanced cancer patients with doses higher than those clinically administered to characterize the dose-dependent effects of sunitinib on QT/QT_c interval. It presents QT/QT_c interval data of study drug concentrations, both therapeutic and suprathreshold concentrations, through robust serial electrocardiogram assessments. The study uses a unique ICH E14-compliant design that relies on the accumulated nonclinical and clinical data, and presents an alternative to conventional thorough QT trials outlined in the ICH E14 guidance.

growth factor receptors (PDGFR- α and PDGFR- β), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor (CSF-1R), and glial cell-derived neurotrophic factor receptor (REarranged during Transfection; RET; refs. 3–9). Consequently, sunitinib exhibits potent and direct antiangiogenic and antitumor activity. Sunitinib has been approved internationally for the treatment of advanced renal cell carcinoma and imatinib-resistant or imatinib-intolerant gastrointestinal stromal tumors. Sunitinib is metabolized by cytochrome P450 (CYP), CYP3A4, to produce the active metabolite, SU012662, which exhibits similar pharmacologic properties to sunitinib and is also metabolized by CYP3A4 (10). Coadministration of sunitinib with strong inhibitors or inducers of CYP3A4, such as ketoconazole or rifampin, could result in plasma concentrations which are approximately doubled or halved, respectively (5, 11, 12). The maximum plasma concentration (C_{max}) generally occurs between 6 and 12 hours (T_{max}) following administration, and exposure increases linearly from 25 to 350 mg. Given the prolonged terminal half-lives of sunitinib and SU012662 of ~40 to 60 hours and 80 to 110 hours, respectively, sunitinib and SU012662 accumulate 3- to 4-fold and 7- to 10-fold with repeated daily administration. Steady state concentrations are achieved within 10 to 14 days, and by day 14, combined plasma concentrations of sunitinib and its active metabolite (total drug) range from 62.9 to 101 ng/mL. Pre-clinical studies have indicated that concentrations >50 ng/mL are required to inhibit receptor phosphorylation and result in antitumor activity (5). A phase I study showed the safety of achieving steady state/therapeutic concentrations after a single 150 mg loading dose on day 1, providing the rationale for the design of this study (13).

Before the initiation of clinical trials, the effects of sunitinib on cardiac conduction were identified in *in vitro* and *in vivo* pharmacology studies. Single high doses of sunitinib (50 and 150 mg/kg) prolonged the QT_c interval (by 72 and 77 ms, respectively), compared with controls from *in vivo* studies of healthy telemetered monkeys (8). QT interval prolongation was observed at nighttime, 11 to 14 hours after sunitinib administration. However, during daylight, a relatively higher heart rate could have masked a QT effect (14–17). In this study, the combined plasma concentration 6 hours after dosing for sunitinib and SU012662 was 288 to 326 ng/mL (65.2 ng/mL unbound plasma concentration of sunitinib + SU012662). Animals treated with sunitinib at 50 and 150 mg/kg appeared fully recovered 24 hours after treatment, although arterial blood pressure remained slightly higher than control levels (8).

In a separate study in monkeys, repeated doses of sunitinib (6 and 12 mg/kg), achieving steady state plasma concentrations similar to those observed in patients treated with repeated 50 mg daily doses, have shown no evidence of QT_c prolongation (8). Blockade of the human ether α -go-go potassium ion channel by sunitinib (IC₅₀ = 108 ng/mL) and SU012662 (IC₅₀ = 1,300 ng/mL) was observed *in vitro* (8). Consistent with this effect, sunitinib treatment resulted in the prolongation of the action potential duration in a dog with isolated Purkinje fibers at concentrations of >1 μ mol/L (400 ng/mL). In the same assay, treatment with SU012662 affected the cardiac action potential morphology at concentrations of >400 ng/mL (8), which seemed to be consistent with effects on the calcium and sodium ion channels (18).

In the present study, a novel International Conference on Harmonization E14-compliant design was used to assess the effects of high concentrations of sunitinib on the QT interval in patients with advanced solid tumors. This single-treatment arm, nonrandomized design used loading doses at the beginning and end of a 1-week daily dosing regimen to achieve the required high concentrations of sunitinib and SU012662 (>180 ng/mL; approximately double the therapeutic concentrations). This regimen allowed the effects of sunitinib on QT/QT_c interval to be assessed at both steady state/therapeutic and suprathreshold concentrations and provided additional safety information in the intended patient population at higher exposures than are normally achieved clinically. This novel design provides an alternative to a conventional TQT trial and presents an attractive model for the design of future QT oncology trials.

Materials and Methods

Study design

The study used a single-arm, blinded design. The primary objective of the study was to assess the effects of high peak plasma concentrations of sunitinib and SU012662 on the QT_c interval in patients with advanced solid tumors. Secondary objectives included assessing the safety and tolerability of sunitinib and the concentration-effect relationship between the QT and QT_c interval, and pharmacokinetic (PK) parameters for sunitinib and SU012662. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines. The study was approved by the institutional review board at the participating center.

Study population

Patients (ages ≥ 18 y) with histologically proven advanced solid tumors were enrolled into the study and met the following inclusion criteria: resolution of all acute toxic effects of prior chemotherapy, radiotherapy, cytokine therapy, or surgical procedures to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade ≤ 1 (19), Eastern Cooperative Oncology Group performance status of 0 or 1 (20), and left ventricular ejection fraction $\geq 50\%$ without support from cardiotropic agents, and room air oxygen saturation by pulse oximeter $>95\%$. All patients had adequate hematologic, hepatic, renal, and cardiac function. Patients were excluded if they had previous therapy for malignancy within 21 d before day -1, had received any known CYP450 enzyme-inducing/inhibiting agents or any medication known to cause QT_c prolongation within 2 wk of day -1, had extensive prior anthracycline exposure, prior trastuzumab therapy, or any of the following within the prior 12 mo: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis, clinically symptomatic, and uncontrolled cardiovascular disease, ongoing cardiac dysrhythmias of NCI CTCAE v.3.0 grade ≥ 2 , atrial fibrillation, or prolongation of the QT_c interval to >430 ms in men or >450 ms in women. All patients provided informed written consent before participating in the study.

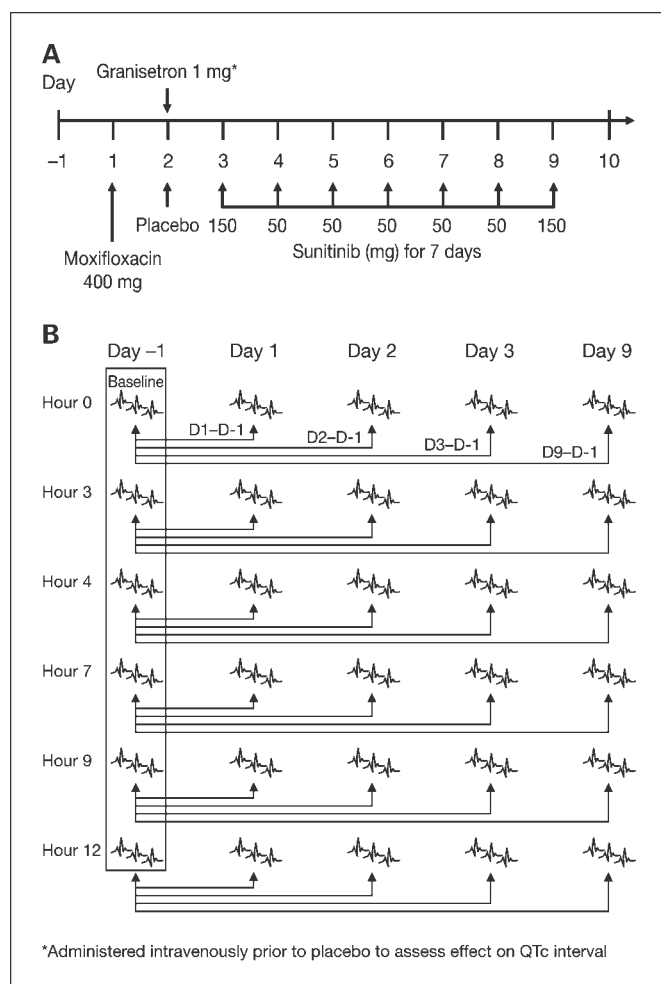


Fig. 1. A, treatment with moxifloxacin (day 1; 400 mg), placebo (day 2), and sunitinib (days 3 and 9; 150-225 mg). B, ECG evaluations (triplicate) time-matched to those on day -1 (evaluable population; $n = 24$). The pre-dose ECG on days 1, 2, and 3 also served as the 24-h post-dose for days -1, 1, 2, 3, and 4.

Treatment

The treatment schedule is summarized in Fig. 1A. All patients received a single oral dose of 400 mg of moxifloxacin on day 1 as a positive control for QT_c prolongation (21, 22). Placebo was administered orally on day 2. On day 3, a 1-wk course of sunitinib was initiated orally by administering a 200 mg loading dose. This was followed by 50 mg of oral maintenance doses on days 4 to 8; patients self-administered study medication on days 5 to 8. A second loading dose was administered on day 9. If more than two of the first six patients treated at the 200 mg loading dose experienced a dose-limiting toxicity, the loading dose was reduced to 175 mg. If two of the next six patients treated at the 175 mg loading dose experienced a dose-limiting toxicity, the loading dose was further reduced to 150 mg. The maintenance dose on days 4 to 8 remained at 50 mg daily regardless of the loading dose. If none of the first six patients treated at the 200 mg loading dose experienced a dose-limiting toxicity, the loading dose was increased to 225 mg. At the 225 mg loading dose, if one patient experienced a dose-limiting toxicity, the loading dose was reduced to 200 mg, and enrollment completed at a 200 mg loading dose. A replacement patient was enrolled for each patient who required a dose reduction to collect enough data at suprathreshold levels. Meals for all patients were matched in quantity, consumed at identical times, and given at least 2 h before any ECG on days -1, 1, 2, 3, and 9. Because of expected frequency of gastrointestinal side effects (nausea/vomiting) with sunitinib, 1 mg of granisetron i.v. was administered before dosing on days 3 and 9 (a saline placebo was administered on days -1 and 1). To assess the effect of granisetron on QT_c interval, granisetron (1 mg i.v.) was also administered before placebo dosing on day 2. If nausea and vomiting persisted, a second injection of granisetron could be administered. However, patients were subsequently withdrawn from the study and replaced to ensure that enough subjects were available for the analysis. Patients were allowed to take oral granisetron, not above the recommended dose, on days 4 to 8. Loperamide was permitted for treatment or prophylaxis of diarrhea.

Continuation of sunitinib

After completion of the protocol, patients who tolerated sunitinib treatment and did not experience disease progression were allowed to continue treatment on an extension protocol.

PK assessments

Complete PK profiles for sunitinib, SU012662, and total drug were obtained on days 3 and 9. Blood samples (4 mL samples) were collected following ECGs and vitals assessment at pre-dose (0 h), and 3, 4, 7, 9, 12, and 24 h post-dose. On day 9, additional samples were collected 72 and 168 h post-dose (on days 12 and 16). Blood samples were centrifuged and plasma concentrations of sunitinib and SU012662 were determined using liquid chromatography-tandem mass spectrometry, as previously reported (23, 24). PK parameters (C_{max} , T_{max} , AUC_{0-24} , and C_{trough}) were determined using WinNonlin version 3.2 (PharSight, Corp.).

ECG assessments

Triplicate (three ECGs 2 min apart) 12-lead ECGs were done at screening. Serial triplicate standard 12-lead ECGs were obtained on days -1, 1, 2, 3, and 9 at the matching clock times corresponding to pre-dose (25 min before dosing time), and 3, 4, 7, 9, and 12 h post-dose (Fig. 1B). The pre-dose ECG on days 1, 2, and 3 also served as the 24 h post-dose for days -1, 1, and 2. A triplicate ECG was obtained 24 h after sunitinib dosing on day 3 and before the sunitinib maintenance dose on day 4, as well as 24 h (day 10) after the last sunitinib loading dose on day 9. Additional triplicate ECGs were obtained on post-sunitinib treatment on days 12 and 16 (72 and 168 h after dosing on day 9). Three methods were used for heart rate correction of QT in this study. The correction method used for the primary end point was Frederica's method (QT_cF; ref. 25). Secondary end

points included correction using Bazett's method (QT_B; ref. 26), a study-specific correction (QT_S; ref. 27).

Safety and tolerability assessments

Safety and tolerability were assessed by monitoring adverse events (AE) after dosing on day 1 until the final visit. AEs were graded according to NCI CTCAE version 3.0 (19).

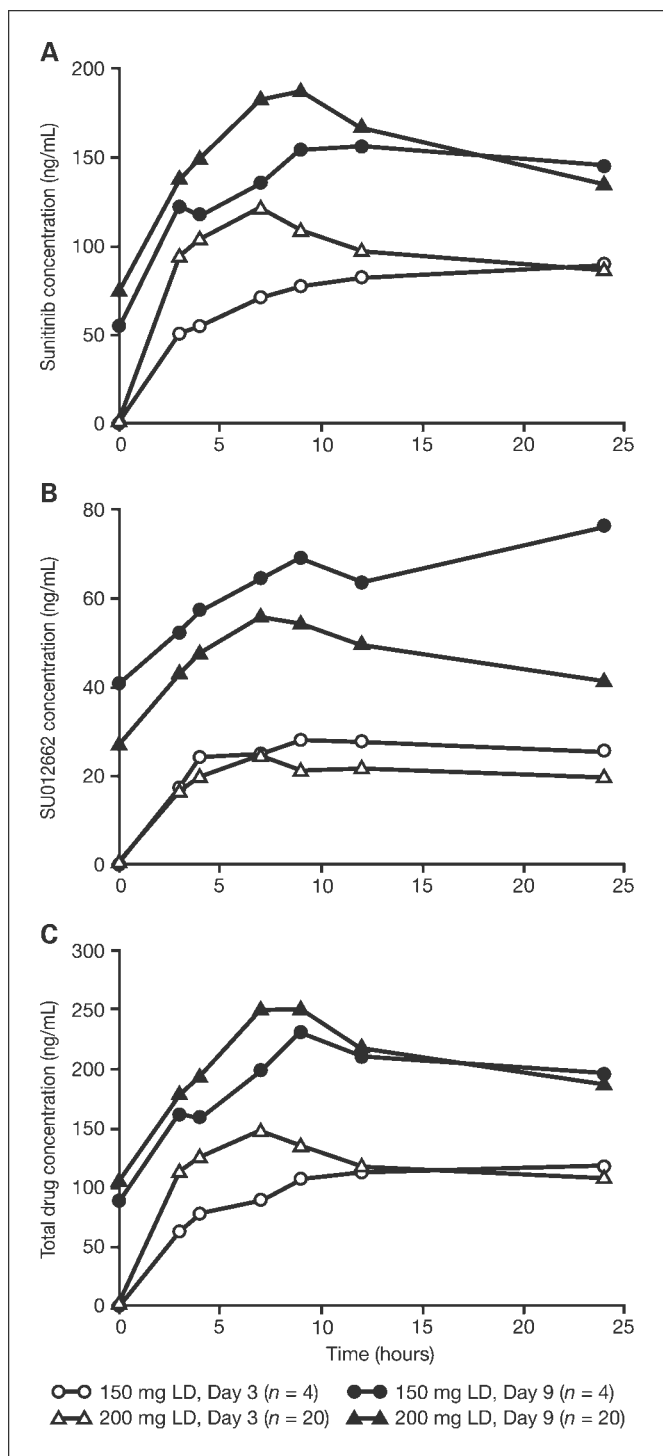


Fig. 2. Median plasma concentration-time profiles of sunitinib (A), its active metabolite SU012662 (B), and total drug (C; evaluable population; n = 24) following a loading dose (150 mg, n = 4; or 200 mg, n = 20) administered on days 3 and 9.

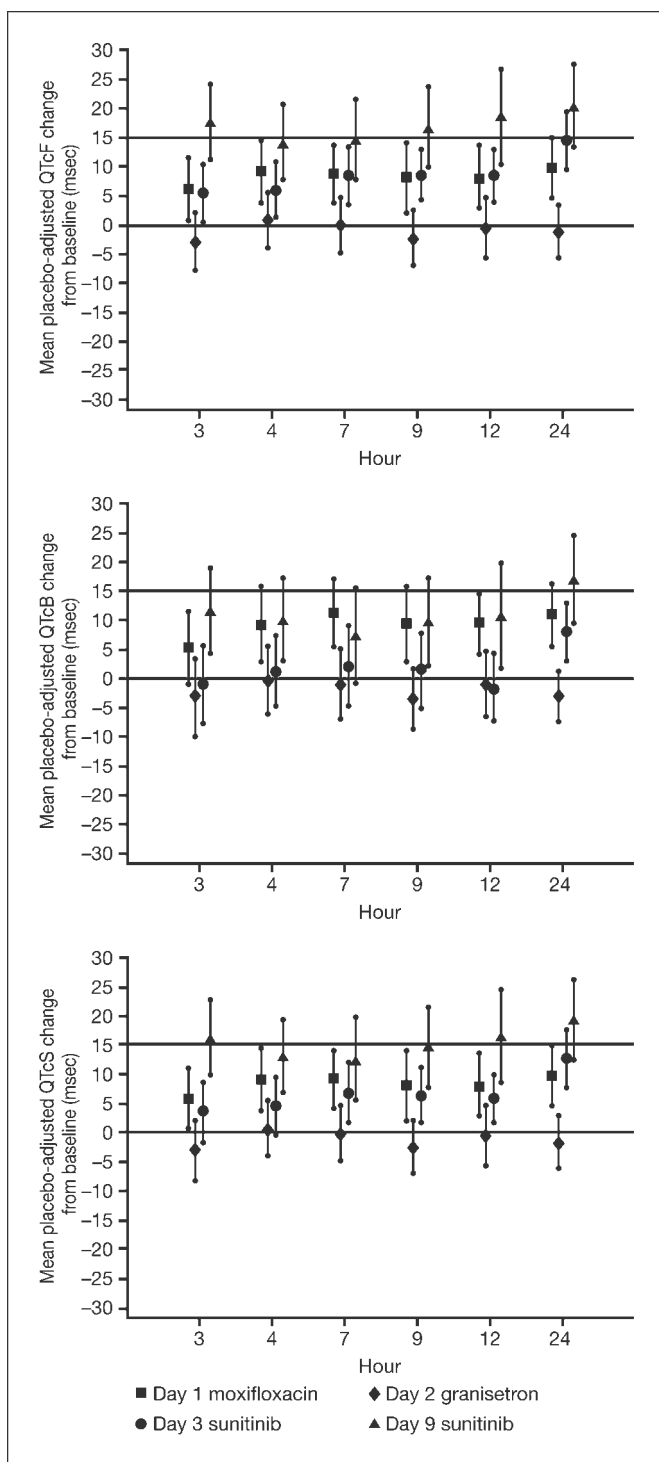


Fig. 3. Mean (90% CI) placebo-adjusted QT_cF, QT_cB, and QT_cS changes from baseline versus time for all patients studied.

Statistical analysis

Sample size determination. Based on QT/QT_c interval data from previous studies with sunitinib in patients with advanced solid tumors (8), a sample size of 30 evaluable patients was considered sufficient to detect at least an 8 ms difference for each treatment in the mean change from baseline in QT_cF (based on α = 0.05 and a power of 80% using a one-sided t test and an estimated SD of 16 ms).

Study populations. With the exception of safety findings, results reported are for the evaluable patient population, which was defined as those who completed all dosing and all of the planned PK and ECG assessments up to day 10. Additionally, a patient's drug concentrations on day 9 were required to be >180 ng/mL, regardless of loading dose, which is approximately double the steady state/therapeutic concentration. The safety population comprised all patients enrolled in the study who received at least one dose of any study medication.

QT/QT_c analysis. The average of triplicate ECG measures at each time point for each patient was used for analyses. The placebo-adjusted change from time-matched, pre-dose baseline in QT_cF, QT_cB, and QT_cS interval at each time point (3, 4, 7, 9, 12, and 24 h) on days 3 and 9 were calculated [day 3 or 9 - (day 2 to day -1)] and assessed using the linear model (PROC MIXED in SAS) for the evaluable population. This model included factors accounting for the following sources of variation: baseline, gender, and treatment. Least-squares means, SEs, *P* values, and two-sided 90% confidence intervals (CI) were summarized.

PK/pharmacodynamic analysis. The relationship between concentrations of sunitinib, SU012662, total drug, and placebo-adjusted QT_cF change from baseline for days 3 and 9 was assessed. This relationship was assessed using all available paired PK/ECG time points. Descriptive statistics (*n*, mean, SD, coefficient of variation, median, minimum, maximum) for the maximum placebo-adjusted QT_cF change from baseline and the time of maximum placebo-adjusted QT_cF change from baseline on days 3 and 9 were calculated.

Results

Patient disposition and baseline characteristics

A total of 48 patients were enrolled in the study and comprised the safety population. Patients in the safety population had a median age of 60 years (range, 20-87); 52% were male and 88% were white. All patients had received prior surgery, 17 (35%) had received prior radiotherapy and 41 (85%) had received prior systemic therapy. Eastern Cooperative Oncology Group performance status at baseline was 0 in 13 (27%) and 1 in 35 (73%).

Three patients discontinued due to AEs [grade 3 syncope on day 10 (*n* = 1) and events related to underlying disease (*n* = 2)

on days 1 and 6] and one discontinued on day 7 due to lack of efficacy. Forty-four (92%) patients received all drug treatments. A total of 24 patients completed all PK and ECG assessments up to day 10, and were evaluable for the primary analysis. Despite larger initial projections, 24 patients were sufficient to detect a statistical difference in the moxifloxacin control. Patient baseline characteristics in the evaluation population was median age, 61 years (range, 31-79), 37% male and 79% white. Six of the 24 (25%) were classified as Eastern Cooperative Oncology Group performance status 1 at baseline.

PK for sunitinib, SU012662, and total drug

The plasma profile values of median sunitinib, SU012662, and total drug in the evaluable population (*n* = 24) following a loading dose (150 mg, *n* = 4; or 200 mg, *n* = 20) administered on days 3 and 9 are presented in Fig. 2. PK parameters were as expected and were not affected by the administration of granisetron or moxifloxacin. Concentrations increased from day 3 to 9 and between dose levels. Mean *C*_{max} for total drug achieved on day 3 were 122 and 164 ng/mL after the 150 and 200 mg loading doses, respectively. Both values are within the therapeutic range achieved with the recommended dose of 50 mg daily (7, 24, 28). On day 9, mean *C*_{max} for total drug was 243 and 271 ng/mL following the 150 and 200 mg loading doses, respectively. These were approximately twice the expected therapeutic concentration (7, 24, 28). Median *T*_{max} for total drug was observed 7.2 to 10.6 hours following sunitinib administration.

Corrected QT intervals

For the evaluable population, the QT_cF at the day -1 baseline time point was 411.8 ms (SD = 17.8 ms). The respective values for QT_cB and QT_cS were 425.3 ms (SD = 20.6 ms) and 415.2 ms (SD = 17.7 ms). Moxifloxacin administration on day 1 increased QT_cF by 5.6 ms (90% CI, 1.9-9.3), which was within the expected range (22, 29, 30). The increase in QT_cB with moxifloxacin was 11.1 ms (90% CI, 5.3-16.9) and the observed prolongation of QT_cS was 5.7 ms (90% CI, 2.0-9.4). The maximum mean change

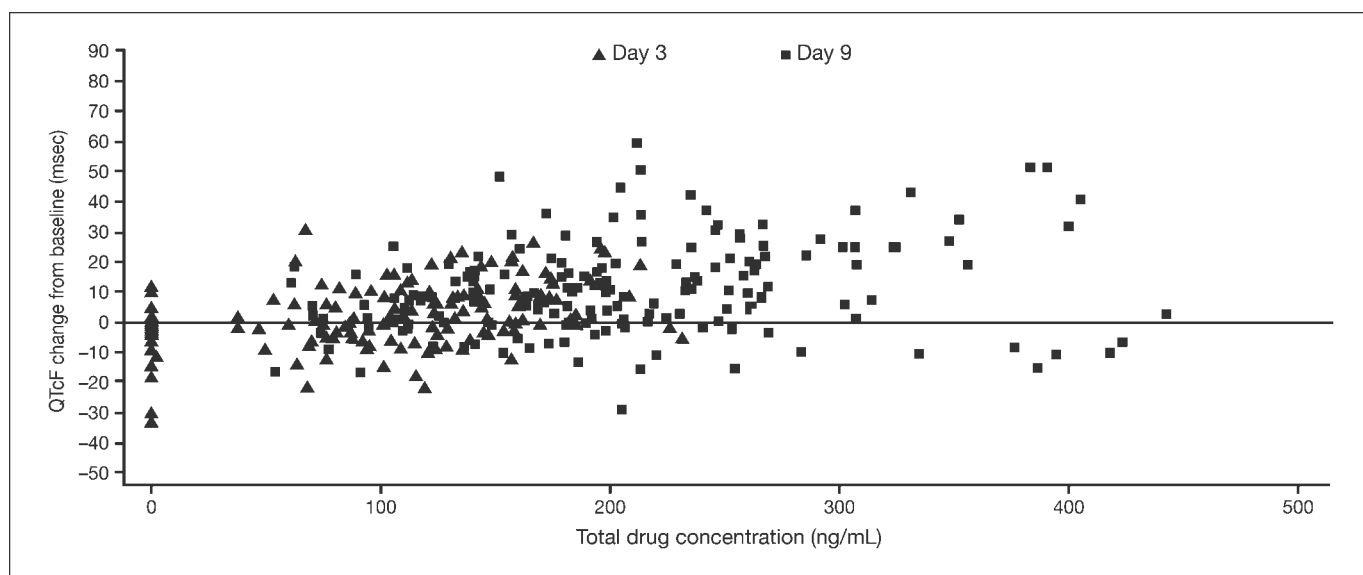


Fig. 4. Scatter plot of individual placebo-adjusted QT_cF changes from baseline versus total drug concentrations for the evaluable population. Mean *C*_{max} = 129 and 202 ng/mL for days 3 and 9, respectively.

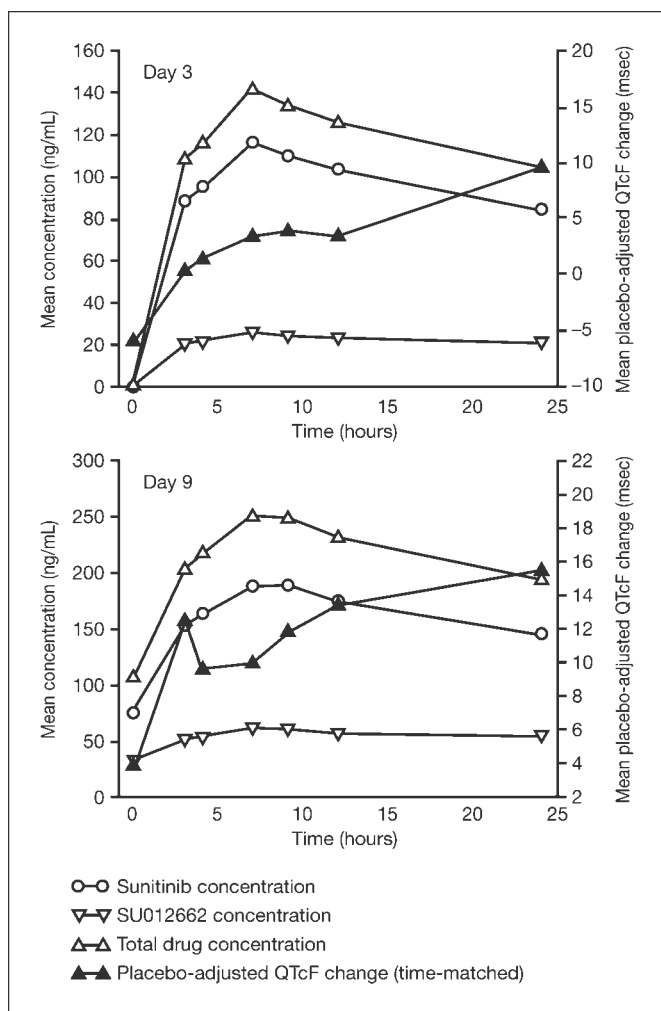


Fig. 5. Overlay plot of mean sunitinib, SU012662, and total drug concentrations and mean placebo-adjusted QT_cF changes from baseline versus time for all sunitinib loading doses combined: evaluable population (days 3 and 9).

obtained was >5 ms and the 90% CIs had a lower limit of >0 ms, regardless of the population or baseline correction method.

On day 3, the maximum placebo-adjusted, time-matched QT_cF prolongation at 24 hours post-dose was 9.6 ms (90% CI, 4.1-15.1), and the respective values for QT_cB and QT_cS were 7.9 ms (90% CI, 3.0-12.8) and 7.4 ms (90% CI, 2.4-12.5). No effect was observed at any other time on day 3. Supratherapeutic doses of sunitinib on day 9 resulted in prolonged QT_c values. The maximum placebo-adjusted, time-matched QT_cF prolongation was 15.4 ms (90% CI, 8.4-22.4) on day 9 (recorded at 24 hours post-dose; Fig. 3). The respective values for QT_cB and QT_cS were 16.8 ms (90% CI, 9.3-24.2) and 13.9 ms (90% CI, 7.0-20.9).

QT_c prolongation with sunitinib (based on absolute values) occurred more frequently in females than in males, 20% versus 0% (for QT_cF increases of >450 but ≤480 ms) and 6.7% versus 0% (for QT_cF increases of >480 but ≤500 ms). The respective values for QT_cB were 33.3% versus 11.1% and 6.7% versus 0%; and those for QT_cS were 20% versus 0% and 6.7% versus 0%. None of the patients developed grade ≥3 QT_cF prolongation (>500 ms; NCI CTCAE version 3.0) at therapeutic or supratherapeutic concentrations. Two patients had a grade 1

QT_cF change from baseline (>450 to 470 ms; ref. 24) on day 3. On day 9, two patients had grade 1 QT_cF prolongations and two had grade 2 prolongations (one patient with >470 to 500 ms and one with an increase of ≥60 ms; ref. 19). Granisetron had no significant effect on QT_c interval duration. The maximum mean placebo-adjusted, time-matched QT_cF prolongation observed with granisetron was 2.0 ms (90% CI, -0.1 to 4.2).

PK/pharmacodynamic (ECG) relationship. There was an increase in QT_cF response with increasing total drug concentrations (Fig. 4). Placebo-adjusted QT_cF changes correlated with C_{max}, AUC₀₋₂₄, and C_{trough} for sunitinib, SU012662, and total drug. Overlay plots show that the time of maximum placebo-adjusted QT_cF change from baseline did not correspond well with T_{max} for sunitinib, SU012662, and total drug (Fig. 5). A similar trend was seen on an individual patient level. The median time of maximum placebo-adjusted QT_cF change occurred 10.5 to 24 hours post-dose on days 3 and 9, later than the median T_{max} for sunitinib, SU012662, or total drug (7.2-10.6 hours). QT_cB and QT_cS had similar results.

Adverse events

Sunitinib was generally well tolerated, and most patients (79%) had AEs that were grade 1 or 2. Forty-seven patients (98%) experienced AEs and 43 (91%) experienced AEs considered to be related to the study drug. The most common AEs included nausea (38% of patients), fatigue (34%), hypertension (26%), constipation (26%), and anorexia (21%; Table 1). Seven patients experienced at least one grade 3 AE. These included hypotension, diarrhea, fatigue, syncope, hypertension, thrombocytopenia, leukopenia, and neutropenia. Six patients experienced a serious AE, including one patient with treatment-related serious AEs (syncope and fatigue; non-treatment-related serious AEs were small bowel obstruction, hypotension, new brain lesions, nausea, vomiting and gait disorder, and disease progression). Four patients experienced a total of five AEs which resulted in study discontinuation. One patient discontinued due to treatment-related grade 3 syncope. Three patients discontinued

Table 1. Adverse events reported in ≥9% of patients, regardless of causality

Adverse event	No. of patients (N = 48)	
	Grade 1/2, no. (%)	Grade 3, no. (%)*
Skin discoloration	28 (60)	0
Nausea	18 (38)	1 (2)
Fatigue	16 (34)	1 (2)
Constipation	12 (26)	0
Hypertension	12 (26)	1 (2)
Anorexia	10 (21)	0
Diarrhea	10 (21)	1 (2)
Thrombocytopenia	7 (15)	1 (2)
Arthralgia	6 (13)	0
Vomiting	6 (13)	1 (2)
Back pain	6 (13)	0
Headache	6 (13)	0
Dizziness	5 (11)	0
Dyspepsia	5 (11)	0
Mucosal inflammation	5 (11)	0

*No grade 4/5 events were reported for the toxicities listed.

treatment due to AEs considered to be related to underlying disease including left-arm numbness, new brain lesions, abdominal pain, and disease progression.

No ECGs were deemed to be abnormal by the investigator or consulting cardiologist, and no cardiac arrhythmias were reported. Two patients experienced a nonserious potentially cardiac-related AE: grade 1 tachycardia on day 4 that was not considered to be related to treatment (the patient died of progressive disease on day 7) and grade 1 bradycardia on day 5 that was treatment-related (the patient recovered).

Discussion

The evaluation of a drug's potential to prolong the QT interval is expected in oncology drug development. Seven of eight original new drug applications submitted to the Food and Drug Administration during 2006 to 2007 contained QT evaluations. Compared with these, the sunitinib new drug application (submitted at the end of 2005) was the only application to include a dedicated blinded QT trial incorporating both a positive and placebo control (31). Results indicated that sunitinib caused a dose-dependent prolongation of the QT interval at steady state/therapeutic concentrations on day 3 (9.6 ms; 90% CI, 4.1-15.1 for QT_{cF}) with the placebo-adjusted, time-matched correction. After suprathreshold doses (150-200 mg) on day 9, the maximum mean prolongation of QT_{cF} changes following sunitinib administration were correlated with exposure to sunitinib, SU1012662, and total drug, but the time of maximum QT_{cF} change did not correlate well with T_{max} , suggesting that there may be a lag time for the effect of QT_{cF}. A similar pattern was noted in monkey studies with sunitinib that showed a QT effect during nighttime, when heart rates were lower, several hours after the expected C_{max} (8). QT_{cF} outlier values of >450 ms were higher in females than males; although the numbers are too small for formal analyses, it should be noted that females at entry had higher QT inclusion criteria values than men (≤ 450 versus ≤ 430 ms), which led on average to a 3 to 6 ms QT_c difference depending on the correction method. No patient had a QT_{cF}, QT_{cB}, or QT_{cS} value >500 ms (NCI CTCAE version 3.0 grade ≥ 3 prolongation). Consistent with previous reports (32-34), concomitant treatment with granisetron resulted in a negligible effect on the QT interval. Treatment with moxifloxacin (active control) produced QT_{cF}, QT_{cB}, and QT_{cS} prolongations in the expected range (22, 29, 30), suggesting that the study design was valid and had adequate sensitivity to detect a significant increase in the QT interval. AEs observed in this trial were consistent with those for sunitinib in previous clinical studies (10, 35).

Anticancer drugs present a challenge for QT_c interval prolongation assessments because the standard criteria outlined in the E14 guidance, such as study in healthy volunteers or use of a placebo-based crossover design, often cannot be met. The present study would have been difficult to conduct in healthy volunteers. Furthermore, a clinical trial in patients with advanced cancer using a placebo-based, crossover design may be unethical

or unfair to its subjects. Even when simplified for this patient population, patient compliance, serial PK and ECGs, and the onset of AEs or progressive disease make the conduct of E14-compliant trials difficult. Notably, despite the simplified design, only 50% of the enrolled patients were considered evaluable, further underlying the difficulty of conducting these trials in patients with cancer.

The potential for QT prolongation was identified in early *in vitro* and *in vivo* pharmacology studies with sunitinib, as part of the standard battery of nonclinical cardiovascular assessment. The PK and safety results of early clinical trials (13, 24, 36, 37) provided valuable information which aided the design and conduct of this study. Importantly, these early data identified the PK basis for the use of a loading dose to achieve supratherapeutic concentrations, enabled a short and tolerable duration of high exposure (1 week) and provided evidence for the prophylactic use of antiemetics for nausea and vomiting. Using the available clinical data from more than 500 patients across several trials provided additional safety and PK data that contributed to this novel design and an adequate sample size to achieve statistical significance.

The safety profile and AEs observed during sunitinib administration were consistent with those reported (38), and were acceptable and manageable. At the dose and schedule used in this study, granisetron did not produce significant QT_c prolongation, but did prevent major gastrointestinal distress without confounding the ECG evaluations even after high doses of sunitinib. Additionally, prevention of nausea and vomiting may be important, as resulting electrolyte disturbances could lead to QT_c interval prolongation.

In the current trial, none of the patients developed QT_c interval prolongation values that were severe or >500 ms (NCI CTCAE grade ≥ 3). Indeed, in >5,000 patients treated who had regular baseline and on-treatment ECGs, <2.3% reported a QT_c interval prolongation of NCI CTCAE grade ≥ 3 . Torsade de pointes has been observed in <0.1% of sunitinib-exposed patients. Nevertheless, monitoring may be particularly important in patients with a history of QT interval prolongation, patients taking antiarrhythmics or individuals with relevant preexisting disease (e.g., bradycardia, electrolyte imbalances; ref. 39). Periodic monitoring of electrolytes, particularly potassium and magnesium, and on-treatment ECGs should be considered for patients receiving sunitinib. In conclusion, our results suggest that sunitinib has a dose-dependent effect on QT interval. The increased risk of ventricular arrhythmias must be weighed against the therapeutic benefit sunitinib provides to patients with advanced cancer (40, 41).

Disclosure of Potential Conflicts of Interest

C. Bello, X. Huang, S. Patyna, M. Toh and C. Baum, current or former employees, Pfizer, Inc. M. Mulay, speakers' bureau, Pfizer. L. Rosen has received research support to cover costs for this clinical trial from Pfizer. The other authors declare that they have no potential conflicts of interest.

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