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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Sutent®/sunitinib malate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00226811

PROTOCOL NO.: A6181054

PROTOCOL TITLE: An Open Label International Multi-Center Phase 2 Activity and Safety Study of SU011248 in Patients with Advanced/Metastatic Gastric Cancer Progressing or Recurring after One Prior Chemotherapy.

Study Centers: China (4 centers), Hong Kong (2 centers), Italy (2 centers), Japan (3 centers), Republic of Korea (4 centers), Portugal (2 centers; 1 did not randomize subjects), Taiwan (2 centers)

Study Initiation and Completion Dates: 31 January 2006 to 27 May 2008

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To determine the antitumor activity of single agent sunitinib at a dose of 50 mg orally once daily for 4 consecutive weeks repeated every 6 weeks in subjects with advanced/metastatic gastric cancer, after failure of one prior chemotherapy regimen for advanced/metastatic disease.

Secondary objectives:

- To assess measures of clinical benefit and duration of tumor control.
- To evaluate the safety and tolerability of sunitinib.
- To explore the effects of sunitinib on patient-reported outcomes of health related quality of life (HRQoL) and gastric cancer specific symptoms.
- To evaluate sunitinib and SU012662 trough concentrations (C_{trough}) and to correlate these plasma concentrations with activity and safety parameters.

- To explore the correlations of cancer biomarkers with cancer- and treatment-related outcomes.

METHODS

Study Design: This was an open-label, uncontrolled, multicenter, Phase 2 study evaluating the activity and safety of single-agent sunitinib in subjects with locally advanced or metastatic gastric cancer that had progressed or recurred after treatment with a prior chemotherapy for locally advanced or metastatic disease.

The study consisted of 2 parts:

Part 1: This part of the study followed a 2-stage Simon design. If ≤1 objective responses (complete response, CR, or partial response, PR) were observed in the first 38 eligible subjects, then the study would end. If ≥2 of these subjects achieved a CR or PR, then the study was planned to proceed to Stage 2 by enrolling 25 additional subjects. Subject enrollment in Stage 1 could temporarily have been kept on hold until the number of objective responses required in Stage 1 for study continuation to Stage 2 was observed. If at least 7 of 63 eligible subjects demonstrated a CR or PR or if clinically meaningful results from other efficacy time-to-endpoints (overall survival [OS] or progression-free survival [PFS]) were observed (compared with historical controls), then the study was planned to proceed to Part 2.

Part 2: The sample size for Stage 2 of the study was determined by the local registration in respective countries. The overall sample size was planned to be up to 160 subjects. Of these, at least 60 Chinese and 40 Korean subjects were planned to be enrolled in the study for local registration in respective countries.

Sunitinib was administered orally daily for 4 weeks followed by a 2-week off-treatment period (Schedule 4/2) in each cycle. The starting dose was 50 mg daily with provision for dose interruption and/or reduction based on tolerability. All subjects received repeated cycles of sunitinib until disease progression, occurrence of unacceptable toxicity, withdrawal of subject consent, or other withdrawal criteria were met. After discontinuation of treatment and the mandated 28-day follow-up, subjects were followed in order to collect information on further antineoplastic therapy and survival. In subjects discontinuing treatment for reasons other than disease progression, tumor assessment continued until disease progression, or initiation of another antineoplastic therapy.

Number of Subjects (Planned and Analyzed): Thirty-eight subjects were planned to be treated in Part 1 of the study. If ≥2 of the subjects exhibited responses (PR or CR), the study would proceed to Part 2 and another 25 eligible subjects were to be enrolled. Thirty-eight subjects were enrolled into Part 1 Stage 1 of the study. Two confirmed PRs were achieved, and thus 40 additional subjects were enrolled in Part 1 Stage 2. Enrollment was halted after Part 1 Stage 2 because the minimum number of responding subjects required to proceed to Part 2 was not reached. Further subject enrollment therefore ended after 78 subjects had been enrolled and treated on Part 1. All 78 subjects (100.0%) were analyzed for efficacy, PK and safety. Sixty-four subjects (82.1%) were analyzed for outcomes research.

Diagnosis and Main Criteria for Inclusion: Male or female, 18 years of age or older with Eastern Cooperative Oncology Group (ECOG) performance status ≤1 with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) and a histologically or cytologically confirmed diagnosis of gastric adenocarcinoma or gastroesophageal junction adenocarcinoma (ie, an adenocarcinoma with >50% extension in the stomach); subjects with Stage IV disease not amenable to surgery, radiation, or combined modality therapy with curative intent; subjects previously undergoing local treatment (surgery and/or radiation) with disease that had subsequently progressed or recurred; subjects with disease progression or recurrence after treatment with 1 prior single agent or combination chemotherapy regimen for advanced/metastatic disease (last dose ≥4 weeks before study entry).

Study Treatment: Subjects received open-label sunitinib at a starting dose of 50 mg once daily for 4 consecutive weeks followed by 2 weeks off for a complete cycle of 6 weeks. Sunitinib was taken orally in the morning without regard to meals beginning on Day 1 of the study.

Efficacy Evaluations: The determination of antitumor efficacy was based on objective tumor assessments made according to the RECIST system of 1-dimensional evaluation.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Blood samples for determination of the trough concentrations (predose) of sunitinib and its active metabolite, SU012662, were obtained for subjects in Part 1 of the study on Day 1, 14, and 28, and for a subset of subjects in Part 2 of the study on Day 1 of Cycles 2 and 3, and on Day 28 of Cycles 2, 3, and 5.

Blood samples were collected for the assessment of soluble proteins vascular endothelial growth factor (VEGF), VEGF-C, sVEGFR-2, sVEGFR-3 and stem cell growth factor receptor (sKIT) predose on Day 1, 14 and 28 of Cycle 1, on Day 1 and 28 of Cycle 2, and on Day 28 of Cycle 5. Samples were also taken for the assessment of ribonucleic acid (RNA) expression profiling, circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs). Tumor paraffin blocks could have been optionally provided for analyses of markers that may be associated with tumor proliferation or angiogenesis.

Patient-reported outcomes (PROs) were assessed using the validated self-administered European Organization Research for the Treatment of Cancer (EORTC) quality of life core questionnaire (QLQ-C30) Version 3.0 and gastric cancer module (QLQ-STO22).

Safety Evaluations: Adverse events (AEs) were monitored throughout the study and other evaluations included clinical laboratory tests, electrocardiogram (ECG), vital signs and physical examination.

Statistical Methods: The primary endpoint, objective response rate (ORR), was calculated for the intent-to-treat (ITT) population (ie, subjects receiving at least 1 dose of study drug) of

subjects with the correct histological cancer type and a baseline assessment of disease. A two-sided 95% exact confidence interval (CI) was provided.

Secondary endpoints: clinical benefit response (CBR) rate was calculated for the ITT population of subjects with the correct histological cancer type and a baseline assessment of disease. A two-sided 95% exact CI was provided. Progression-free survival (PFS), time to tumor progression (TTP), and overall survival (OS) were analyzed using Kaplan-Meier methods. PFS and TTP were summarized for the ITT population with the correct histological cancer type and a baseline assessment of disease. OS was summarized for the ITT population overall.

For PROs measured by the EOTRC QLQ-C30 and STO22, descriptive statistics were provided for the absolute domain and single item scores and changes from the baseline (Cycle 1 Day 1 prior to the first dose of study drug). Graphs displaying mean changes were not generated for PROs.

Trough and dose-corrected trough plasma concentrations were summarized graphically and with descriptive statistics by cycle and study day.

The results of biomarker studies (soluble proteins, CECs, CEPs, RNA expression profiling and tumor biopsy results) were reported descriptively and in relation to clinical response and pharmacokinetic (PK) endpoints.

Safety results were reported using descriptive statistics.

RESULTS

Subject Disposition and Demography: Seventy-eight subjects were treated with sunitinib during this study. Seventy six subjects (97.4%) discontinued from the study and 2 subjects (2.6%) completed the study (as indicated on the CRF). A subject was defined as 'complete' if they had been withdrawn from the study with stable disease when the investigator had determined no further clinical benefit was anticipated.

Seventy-six subjects (97.4%) discontinued from the study; 24 (30.8%) discontinued due to an AE (14 subjects [17.9%] due to a treatment-related AE, including 3 deaths, and 10 subjects [12.8%] due to a treatment-unrelated AE, including 5 deaths). Table S1 and Table S2 summarize subject disposition and demographics, respectively.

Table S1. Overall Summary of Subject Disposition and Primary Reason for Discontinuation

Number of Subjects	50 mg Sunitinib
Assigned to Study Treatment	78
Treated	78
Completed	2 (2.6%)
Discontinuations	76 (97.4%)
Subject died	8 (10.3%)
Related to Study Drug	
Adverse Event	8 (10.3%)
Lack of Efficacy	55 (70.5%)
Not Related to Study Drug	
Adverse Event	3 (3.8%)
Subject no longer willing to participate in study	2 (2.6%)

Table S2. Summary of Subject Demographics and Baseline Characteristics

	50 mg Sunitinib N=78
Gender [n (%)]	
Male	56 (71.8%)
Female	22 (28.2%)
Age (years)	
Median	56.0
SD	12.4
Range	25-78
Race [n (%)]	
White	6 (7.7%)
Asian	72 (92.3%)
Weight (kg)	
Median	57.1
SD	9.6
Range	38.5-85.5
Height (cm)	
Mean	166.1
SD	7.8
Range	142.0-180.0
ECOG Performance Status	
0	26 (33.33%)
1	52 (66.67%)
Extent of Disease	
Locally Advanced	5 (6.41%)
Metastatic	73 (93.59%)

Efficacy Results: Among the 78 subjects, 2 subjects (2.6%) achieved a RECIST-defined confirmed PR (95% CI of 0.3% to 9.0%), and 25 subjects (32.1%) had a best RECIST-defined response of stable disease as determined by the investigator (Table S3). In total, 6 subjects (7.7%) had a PR or stable disease lasting ≥24 weeks (CBR) (95% CI of 2.9% to 16.0%).

Overall, the median TTP for the ITT population was 10.1 weeks (95% CI of 7.3 to 11.3 weeks) and the median PFS was 10.0 weeks (95 CI of 6.9 to 11.1 weeks). The median OS for the ITT population was 29.6 weeks (95% CI of 19.1 to 42.0 weeks). The probability of 1-year survival was 24.2% (95% CI of 14.4% to 34.1%).

There were few noticeable changes in most domains of the EORTC QLQ-C30 and QLQ-STO22 during the first 3 cycles of sunitinib treatment (prior to receiving the fourth dose). Those domains that did change were diarrhea after the first and third dose and reflux symptoms after the third dose. Both the domains of diarrhea and reflux symptoms were noticeably worse compared to baseline. At the end of treatment or withdrawal from the study, noticeable changes (deterioration) were observed in most scales and measures of the EORTC QLQ-C30 and QLQ-STO22 compared to the baseline. The domains for perceived financial difficulties, body image, and hair loss did not change noticeably.

Table S3. Best Overall Tumor Response as Determined by the Investigator

Number of Subjects	**50 mg Sunitinib** N=78
Subjects with measurable disease at baseline	78 (100%)
Best Overall Response (%)	
Complete Response (CR)	0
Partial Response (PR)	2 (2.6%)
Stable Disease (SD)	25 (32.1%)
Progressive Disease (PD)	42 (53.8%)
Not Evaluable	5 (6.4%)
Missing[a]	4 (5.1%)
Objective Response (CR+PR)	2 (2.6%)
95% CI	(0.3, 9.0)
Clinical Benefit Rate (CR, PR or SD)[b]	6 (7.7%)
95% CI	(2.9, 16.0)

CI=confidence interval
[a]Subjects had baseline tumor assessments (Appendix B2.2), but did not have subsequent data to allow overall response to be calculated.
[b]Subject with SD best overall response and the duration of SD is ≥24 weeks.

Pharmacokinetic, Pharmacodynamic, and Other Results:

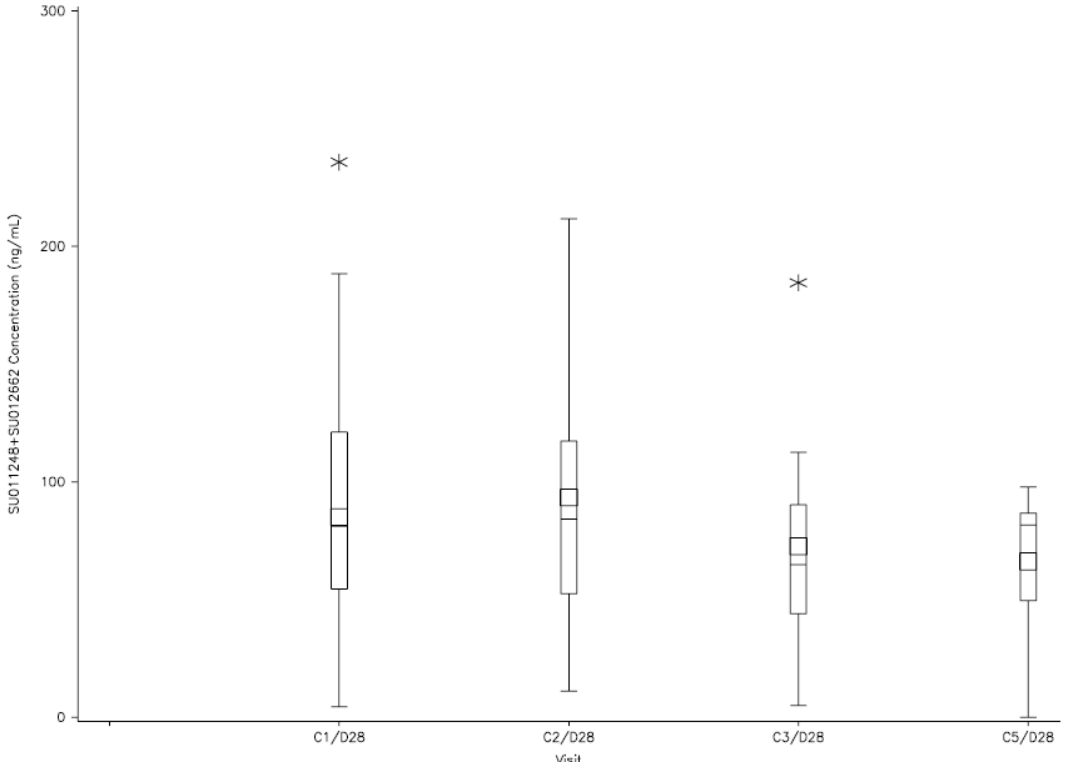
Pharmacokinetics: Mean sunitinib, its metabolite (SU012662), and total drug (sunitinib+SU012662) plasma C_{trough} on Day 28 (steady state) of Cycles 1, 2, 3 and 5 are presented in Table S4. Following intermittent daily dosing of sunitinib (Schedule 4/2; 4 weeks on and 2 weeks off), mean C_{trough} at steady state (Day 28 of Cycles 1, 2, 3 and 5) for sunitinib, its metabolite, and total drug ranged from 45.12 ng/mL to 60.02 ng/mL, 21.12 ng/mL to 33.27 ng/mL, and 66.23 ng/mL to 93.30 ng/mL, respectively. The mean trough plasma concentration box plot of the sunitinib+SU012662 concentration versus cycle day is displayed in Figure S1.

Table S4. Mean (±SD) Sunitinib, SU012662, and Sunitinib+SU012662 Trough Plasma Concentrations on Day 28 of Cycles 1, 2, 3 and 5

Cycle	Day	N[a]	Mean ± SD		
			Sunitinib	SU012662	Sunitinib+SU012662
1	28	67	56.27 ± 31.63	28.77 ± 18.61	85.04 ± 47.67
2	28	40	60.02 ± 29.67	33.27 ± 24.06	93.30 ± 49.71
3	28	17	49.19 ± 29.25	23.47 ± 13.68	72.66 ± 40.91
5	28	6	45.12 ± 24.25	21.12 ± 14.79	66.23 ± 36.25

[a]N: number of subjects with evaluable trough samples

Figure S1. Sunitinib+SU012662 Trough Concentration Versus Cycle Day Box Plot



Pharmacodynamics: Median plasma VEGF concentrations were >2.5-fold above baseline on Day 14 and Day 28 of the first treatment cycle, returning to near baseline levels at the end of the first 2 week off dosing period and increasing again to levels markedly above baseline at Cycle 2 Day 28 and Cycle 5 Day 28. Plasma levels of VEGF-C were below baseline at C1D28 and Cycle 2 Day 28 and were largely unchanged from baseline at other time points. Plasma levels of sVEGFR-2 and sVEGFR-3 declined markedly during Cycle 1, returned partially towards baseline at the end of the 2-week off-dosing period and then declined at the end of Cycles 2 and 5 to levels comparable with those at the end of Cycle 1. Plasma sKIT levels declined progressively during the first 2 cycles of treatment with sunitinib, with no indication of return towards baseline during the off-dosing period.
There were no marked associations between baseline soluble protein levels, or changes from baseline, and measures of clinical outcome for any of the soluble proteins analyzed.

Patient-Reported Outcomes: There were no noticeable changes in most domains of the EORTC QLQ C30 and STO22 during the first 3 cycles of sunitinib treatment (prior to receiving the fourth dose), except for diarrhea after the first and third dose and reflux symptoms after the third dose. Both the domains of diarrhea and reflux symptoms were noticeably worse compared to the baseline. At the end of treatment or withdrawal from the study, noticeable changes (deterioration) were observed in most scales and measures of the EORTC QLQ-C30 and STO22 compared to the baseline. The domains for perceived financial difficulties, body image, and hair loss did not change noticeably.

Safety Results: Seventy eight subjects (100.0%) experienced at least 1 treatment-emergent AE; 77 subjects (98.7%) experienced at least 1 treatment-related AE. The most common treatment-emergent AEs (>15%) in the overall as-treated population were thrombocytopenia (61.5%), neutropenia (52.6%), fatigue (44.9%), anorexia (44.9%), nausea (41.0%), leukopenia (38.5%), anemia (37.2%), diarrhea (35.9%), stomatitis (35.9%), vomiting (30.8%), palmar-plantar erythrodysaesthesia syndrome (28.2%), pyrexia (28.2%), abdominal pain (25.6%), skin discoloration (24.4%), constipation (21.8%), hypoalbuminemia (19.2%), rash (17.9%), hyperbilirubinemia (16.7%) and mucosal inflammation (16.7%).

Fifteen subjects (19.2%) experienced treatment-emergent maximum CTCAE Grade 4 AEs; 12 subjects (15.4%) experienced Grade 4 treatment-related AEs. Overall, 11 subjects (14.1%) experienced Grade 5 treatment-emergent AEs; 4 subjects (5.1%) experienced treatment-related treatment-emergent AEs.

The most common treatment-emergent hemorrhagic AE (experienced by ≥3 subjects) was epistaxis (experienced by 6 subjects [7.7%] all treatment-related).

Thirty subjects (38.5%) were reported to have experienced at least 1 SAE during the study period; 16 subjects (20.5%) had treatment-related SAEs.

In total, 24 subjects (30.8%) permanently discontinued study treatment due to treatment-emergent AEs; 14 subjects (17.9%) had treatment-related AEs. Eight subjects (10.3%) discontinued as a result of death. Nine subjects (11.5%) had a dose reduction due to treatment-emergent AEs, all of which had treatment-related AEs. Thirty-five subjects (44.9%) temporarily discontinued from the study due to treatment-emergent AEs; 32 subjects (41.0%) had treatment-related AEs.

A total of 11 subjects (14.1%) died within 28 days of the last dose of study drug (defined as the "on-study" period); 4 subjects (5.1%) due to treatment-related AEs and 7 subjects (9.0%) due to treatment-unrelated AEs.

Laboratory test abnormalities that were reported as AEs for >2 subjects included AST increased (10 subjects, 12.8%), ALP increased (9 subjects, 11.5%), ALT increased (7 subjects, 9.0%), C-Reactive protein increased (4 subjects, 5.1%), creatinine abnormality (3 subjects, 3.8%), red blood cell count decreased (3 subjects, 3.8%).

During the study, 11 subjects (14.1%) experienced clinically significant changes in vital signs that were reported as AEs of hypertension, 4 with a prior history of hypertension.

Three subjects (3.8%) experienced hypotension, 1 with a prior history of hypertension. Overall, there was no evidence of a change in mean or median QTc interval from baseline considered clinically significant by the investigators.

Table S5 summarizes treatment emergent AEs.

Table S5. Overall Summary of Treatment-Emergent Adverse Events

	50 mg Sunitinib	
Number (%) of subjects	**All-Causality**	**Treatment-Related**
Subjects evaluable for AEs	78	78
Number of AEs	986	696
Subjects with AEs	78 (100.0%)	77 (98.7%)
Subjects with SAEs	30 (38.5%)	16 (20.5%)
Subjects with Grade 3 or 4 AEs	60 (76.9%)	53 (67.9%)
Subjects with Grade 5 AEs	11 (14.1%)	4 (5.1%)
Subjects who discontinued due to AEs	24 (30.8%)	14 (17.9%)
Subjects with dose reduced due to AEs	9 (11.5%)	9 (11.5%)
Subjects with temporary discontinuation due to AEs	35 (44.9%)	32 (41.0%)

AE=adverse event, SAE=serious adverse event

CONCLUSIONS:

- Sunitinib treatment, at a starting dose of 50 mg on Schedule 4/2, did not result in a clinically relevant RECIST-defined ORR in subjects with advanced/metastatic gastric cancer who had previously failed one prior chemotherapy regimen for advanced/metastatic disease.

- The safety profile of sunitinib was generally acceptable and clinically manageable, as the pattern of AEs was generally similar to those reported in other studies of single-agent sunitinib, though the incidence of permanent discontinuations due to treatment-related AEs was 17.9%.

- Health-related quality of life based on available EORTC QLQ-C30 and QLQ-STO22 questionnaire results was maintained by sunitinib treatment during the first 3 cycles of this study, though the domains of diarrhea and reflux symptoms were noticeably worse compared to baseline.

- Trough concentration values for sunitinib and its metabolite SU012662, following a 4/2 dosing schedule in gastric cancer subjects, were consistent with the previously reported PK of sunitinib and SU012662 for the 4/2 dosing schedule and other schedules in Phase 1 and 2 studies of subjects with mRCC, GIST and other solid tumors. No unexpected accumulation of sunitinib and SU012662 was observed throughout the study.

- There were no marked associations between baseline soluble protein levels, or changes from baseline, and measures of clinical outcome in this study.