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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NATIONAL CLINICAL TRIAL NO.: NCT00254540

PROTOCOL NO.: A6181072

PROTOCOL TITLE: Phase II Study of Single-Agent SU-011248 in the Treatment of Patients with Renal Cell Carcinoma

Study Center(s): Twelve (12) centers in Japan

Study Initiation and Completion Dates: 27 December 2005 to 25 February 2009

Phase of Development: Phase 2

Study Objectives:

Primary:

To determine the objective tumor response of single-agent SU-011248 at a dose of 50-mg orally once daily for 4 consecutive weeks and 2 weeks off-treatment, repeated every 6 weeks in renal cell carcinoma (RCC) for the pretreated population (subjects who had previously been treated with one cytokine-based systemic therapy regimen for RCC) and the first-line treatment population (subjects who had not had any prior systemic treatment for RCC).

Secondary:

- To evaluate the safety and tolerability of SU-011248
- To investigate trough plasma concentrations of SU-011248 and its primary active metabolite, SU-012662
- To investigate plasma concentrations of pharmacodynamic markers (soluble proteins of Vascular Endothelial Growth Factor [VEGF] and Soluble VEGFR2 [sVEGFR2]) that may be associated with angiogenesis or tumor pathology
- To assess quality of life (QOL)
- To assess overall survival

METHODS

Study Design: This was an open-label, single-arm, non-randomized, multicenter Phase 2 study evaluating the efficacy and safety of single-agent SU-011248 in subjects with metastatic RCC.

Subjects received SU-011248 in an open-label manner at a starting dose of 50-mg once daily for 4 consecutive weeks followed by a 2-week off-treatment period to form a complete cycle of 6 weeks. Subjects continued to receive SU-011248 until they met any of the study discontinuation criteria.

Screening was performed within 21 days prior to the start of the study treatment. During the study treatment period, observations/tests were performed on Days 1, 14 (up to Cycle 4) and 28 of each cycle. Observation items were subject characteristics, concomitant medications/therapies, treatment compliance, observation of tumor lesions mainly by computed tomography (CT) or magnetic resonance imaging (MRI) scan, answers to EuroQOL EQ-5D (EQ-5D) questionnaire, pharmacokinetic and pharmacodynamic markers, adverse events, hematology, biochemistry, body weight, body temperature, blood pressure, pulse rate, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12-lead electrocardiogram (ECG) and echocardiogram or multigated acquisition (MUGA) scan. A survival survey was conducted once a year for all subjects who received at least one dose of study drug. The survey period lasted from the date of registration of the first subject until 3 years after the completion of subject registration.

Number of Subjects (Planned and Analyzed):

Planned: Fifty-one (51) subjects (26 for the pretreated population and 25 for the first-line treatment population)

Analyzed: A total of 51 subjects composed of 26 for the pretreated population and 25 for the first-line treatment population

Diagnosis and Main Criteria for Inclusion: Subjects aged 20 years or older who had histologically proven RCC with metastases with a component of clear cell histology, evidence of unidimensionally measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST), and past history of nephrectomy. Both subjects who had not received any prior systemic treatment for RCC (first-line treatment population) and those who had been previously treated with only one cytokine-based regimen for RCC (pretreated population) were enrolled in the study.

Study Treatment: Subjects received open-label SU-011248 orally for 4 consecutive weeks followed by a 2-week off-treatment period to form a complete cycle of 6 weeks. SU-011248 was taken orally in the morning without regard to meals beginning on Day 1 of the study. Subjects were monitored for toxicity, and the SU-011248 dose could be adjusted according to individual subject tolerance. Forms and strengths of the study drug were as follows:

- SU-011248 12.5-mg capsule

- SU-011248 25-mg capsule
- SU-011248 50-mg capsule

Efficacy Evaluations: The primary efficacy endpoint was objective response rate (ORR). The ORR was defined as the proportion of subjects with confirmed complete response (CR) or partial response (PR) as the best overall response according to RECIST. To confirm CR or PR, the subject had to meet the criteria for CR or PR at tumor reassessment not less than 4 weeks after the first documentation of response. The secondary endpoints were progression-free survival (PFS), time to tumor progression (TTP), duration of response (DR), time to tumor response (TTR), and overall survival (OS).

Patient-Reported Outcome Evaluations: Health-related quality of life (HRQOL) was assessed using the EQ-5D questionnaire.

Pharmacokinetic and Pharmacodynamic Evaluations: Trough plasma concentrations of SU-011248, its active metabolite, SU-012662, and total drug (SU-011248 and SU-012662) were assessed as pharmacokinetic markers. Plasma concentrations of soluble proteins (VEGF and sVEGFR2) were assessed as pharmacodynamic markers. Plasma samples for pharmacokinetic and pharmacodynamic analyses were collected prior to study treatment on Days 1, 14 and 28 of Cycle 1, Days 1 and 28 of Cycle 2 and Day 28 of Cycle 3.

Safety Evaluations: The measurement and monitoring of adverse events, laboratory test values, subjective symptoms/objective findings, body weight, body temperature, blood pressure, pulse rate, ECOG PS, ECG and echocardiogram or MUGA scan were used to evaluate subject safety.

Statistical Methods: Two analysis sets were defined as follows:

- The Intent-to-Treat (ITT) population was defined as all subjects treated with the study drug at least once. The ITT population was the primary analysis set for efficacy and the analysis set for safety.

- The Per Protocol Set (PPS) was the population which excluded subjects who met at least 1 of the following criteria from the ITT population: subjects who deviate serious inclusion/exclusion criteria or prohibited concomitant medication, subjects who received less than 75% of the planned dose date through all cycles, and finally subjects whom the objective tumor response was not evaluated after study drug dosing. The PPS was the secondary analysis set for efficacy.

In the primary analysis of the primary efficacy endpoint, ORR and its 95% confidence interval (CI) were calculated for each population (pretreated population, first-line treatment population) based on the response according to Extramural Review Committee's assessments. The lower confidence limit was compared with the threshold value considered to be clinically ineffective for each population (10% for the first-line treatment population and 5% for the pretreated population). In the secondary analysis, the same analysis as the primary analysis was performed for investigators' assessments. Furthermore, a subgroup analysis and a logistic regression analysis were performed on the ORR assessed by the

Extramural Review Committee to examine the effects of covariates. In the analysis of the secondary endpoints, descriptive statistics of PFS, TTP, and OS assessed by investigators were calculated using Kaplan-Meier method. A subgroup analysis and a Cox proportional hazards model analysis were also performed to examine the effects of covariates.

In the pharmacokinetic analysis, descriptive statistics were calculated for trough plasma concentrations of SU-011248, SU-012662, and total drug. In the pharmacodynamic analysis, descriptive statistics were calculated for plasma concentrations of pharmacodynamic markers (VEGF and sVEGFR2), and the relationship between the pharmacodynamic markers and antitumor activity was explored by calculating descriptive statistics for the percent change from baseline to each sampling time point for each subgroup based on the best overall response. The percent change from baseline on Day 28 of Cycle 3 was compared among the subgroups based on the best overall response by the Wilcoxon's rank sum test (α=0.05).

In the safety analysis, adverse events, laboratory abnormalities, and other safety parameters were analyzed. The severity of adverse events was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

RESULTS

Subject Disposition and Demography: Subject disposition is shown in Table S1.

Table S1. Subject Disposition and Subjects Analyzed [Number of Subjects (%)]

Population	First-line Treatment	Pretreated	Overall
Enrolled	25	26	51
Treated	25	26	51
Completed	6	4	10 (19.6)
Discontinued	19	22	41 (80.4)
Analyzed for Efficacy			
Intent-to-Treat (ITT) population	25	26	51 (100)
Per Protocol Set (PPS)	15 (60.0)	17 (65.4)	32 (62.7)
Analyzed for Pharmacokinetics	25	26	51 (100)
Analyzed for Pharmacodynamics	25	26	51 (100)
Analyzed for Safety (ITT)	25	26	51 (100)
Adverse events	25	26	51 (100)
Laboratory data	25	26	51 (100)

Of 51 subjects enrolled, 11 subjects (44.0%) in the first-line treatment population and 21 subjects (80.8%) in the pretreated population were males. Mean age was 56.6 years (range: 33 to 76 years) in the first-line treatment population, and 61.1 years (range: 34 to 77 years) in the pretreated population; 7 subjects (28.0%) in the first-line treatment population and 11 subjects (42.3%) in the pretreated population were 65 years or older. Twenty subjects (80.0%) in the first-line treatment population and 22 subjects (84.6%) in the pretreated population had an ECOG PS of 0, and 5 subjects (20.0%) in the first-line treatment population and 4 subjects (15.4%) in the pretreated population had an ECOG PS of 1. In the first-line treatment population and the pretreated population, the median number of cycles was 6.0 cycles and 9.5 cycles, respectively. The median treatment periods (off-treatment

period excluded) were 163.0 days in the first-line treatment population and 192.0 days in the pretreated population.

Efficacy Results: The ORR (95% CI) after the completion of Cycle 4 in the ITT population based on the Extramural Review Committee's assessment, the primary analysis of the primary efficacy endpoint, was 48.0% (95% CI: 27.8 to 68.7%) in the first-line treatment population and 46.2% (95% CI: 26.6 to 66.6%) in the pretreated population. The lower confidence limit for the ORR exceeded the threshold value for each population (10% for the first-line treatment population and 5% for the pretreated population). The ORR (95% CI) after the completion of Cycle 4 in the ITT population based on the investigators' assessments, as the secondary analysis, was 48.0% (95% CI: 27.8 to 68.7%) in the first-line treatment population and 46.2% (95% CI: 26.6 to 66.6%) in the pretreated population. The ORR (95% CI) after the completion of study in the ITT population based on the investigators' assessment was 52.0% (95% CI: 31.3 to 72.2%) in the first-line treatment population and 53.8% (95% CI: 33.4 to 73.4%) in the pretreated population (Table S2).

Table S2. Summary of Objective Response Rate [ITT Population]

Population	First-line Treatment (N=25)	Pretreated (N=26)	Overall (N=51)
After the completion of Cycle 4			
Extramural Review Committee's assessment-based responder [a]	12	12	24
Objective Response Rate (%) [95% CI]	48.0 [27.8, 68.7]	46.2 [26.6, 66.6]	47.1 [32.9, 61.5]
Investigators' assessment-based responder [a]	12	12	24
Objective Response Rate (%) [95% CI]	48.0 [27.8, 68.7]	46.2 [26.6, 66.6]	47.1 [32.9, 61.5]
After the completion of study			
Investigators' assessment-based responder [a]	13	14	27
Objective Response Rate (%) [95% CI]	52.0 [31.3, 72.2]	53.8 [33.4, 73.4]	52.9 [38.5, 67.1]

a) CR or PR
CI = Confidence interval

During treatment with SU-011248 (including 28 days after the completion of treatment) and prior to the start of antitumor therapy other than SU-011248, progressive disease (PD) was experienced by 14 subjects (56.0%) in the first-line treatment population and 18 subjects (69.2%) in the pretreated population. Median PFS was 53.0 weeks and 46.0 weeks for the first-line treatment and the pretreated populations, respectively. Only 1 subject died while on study, but evidence of PD was documented beforehand, and thus TTP and PFS were identical.

According to investigators' assessments, median TTR was 10.0 weeks for the first-line treatment population and 10.5 weeks for the pretreated population. Median DR was 111.6 weeks and 38.1 weeks for the first-line treatment and the pretreated populations, respectively. All-causality death was reported in 14 subjects (56.0%) for the first-line treatment population, and 14 subjects (53.8%) for the pretreated population. Median OS was 143.4 weeks and 141.0 weeks for the first-line treatment and the pretreated populations, respectively.

Patient-Reported Outcome Results: Subjects' HRQOL was evaluated using the EQ-5D questionnaire. For the EQ-5D index score, the range of mean change at each endpoint from baseline was from -0.1573 to 0.0375 in the first-line treatment population and from -0.0974

to 0.0513 in the pretreated population. For the EQ-5D-VAS score, the range of mean change at each endpoint from baseline was from -12.35 to 2.71 in the first-line treatment population and from -11.82 to 4.17 in the pretreated population. Assessment of HRQOL by the EQ-5D questionnaire showed that the EQ-5D index score and EQ-5D-VAS in each cycle trended lower on treatment with SU-011248 and recovered during the off-treatment periods in both subject populations.

Pharmacokinetic and Pharmacodynamic Results: The median plasma trough concentrations of total drug reached therapeutically effective levels estimated from the nonclinical study results (>50 ng/mL) on Day 14 of Cycle 1 in both subject populations, and such levels were sustained during the subsequent treatment period. The plasma trough concentrations of SU-011248 and SU-012662 on Days 14 and 28 of Cycle 1 were comparable to those on Day 28 of Cycles 2-3, which suggested that repeated treatment does not result in further accumulation of the drug in plasma.

Plasma VEGF levels increased and sVEGFR2 levels decreased during treatment with SU-011248, and both VEGF and sVEGFR2 levels nearly returned to baseline during a 2-week off-treatment period. A comparison of the rate of change from baseline to Day 28 of Cycle 3 based on the best overall response by the Wilcoxon's rank sum test (5% significance level) did not reveal statistically significant differences in both subject populations.

Safety Results: An overall summary of adverse events is shown in Table S3.

Table S3. Overall Summary of Adverse Events

Population	First-line Treatment (N=25)		Pretreated (N=26)		Overall (N=51)	
Causality	All-causality	Treatment-related	All-causality	Treatment-related	All-causality	Treatment-related
Number of AE	817	746	956	854	1773	1600
Number of subjects (%)						
AE	25 (100)	25 (100)	26 (100)	26 (100)	51 (100)	51 (100)
AE of Grade 3 or 4	25 (100)	25 (100)	26 (100)	26 (100)	51 (100)	51 (100)
Serious AE [a]	12 (48.0)	11 (44.0)	16 (61.5)	15 (57.7)	28 (54.9)	26 (51.0)
AE of Grade 5	0	0	1 (3.8)	0	1 (2.0)	0
Discontinuation due to AE	6 (24.0)	6 (24.0)	9 (34.6)	7 (26.9)	15 (29.4)	13 (25.5)
Dose Schedule Modification due to AE	22 (88.0)	22 (88.0)	24 (92.3)	24 (92.3)	46 (90.2)	46 (90.2)

AE: Adverse event
a) One subject who developed a SAE after informed consent was obtained, but prior to study drug administration was excluded.

Fifty-one (100%) of 51 subjects had a total of 1773 all-causality adverse events, and 51 (100%) of 51 subjects had a total of 1600 treatment-related adverse events. The most common all-causality adverse events (>20% of subjects in all-causality, any-grade) are summarized in Table S4.

Table S4. Treatment-Emergent Adverse Events Reported in >20% of Subjects [Number of Subjects (%)]

MedDRA Preferred Term (version 11.1)	Total (N=51)
Platelet count decreased	47 (92.2)
White blood cell count decreased	44 (86.3)
Neutrophil count decreased	41 (80.4)
Anorexia	37 (72.5)
Skin discolouration	37 (72.5)
Blood lactate dehydrogenase increased	36 (70.6)
Lipase increased	36 (70.6)
Lymphocyte count decreased	36 (70.6)
Aspartate aminotransferase increased	35 (68.6)
Fatigue	34 (66.7)
Hypertension	31 (60.8)
Pyrexia	31 (60.8)
Diarrhoea	30 (58.8)
Blood creatinine increased	29 (56.9)
Rash	29 (56.9)
Dysgeusia	28 (54.9)
Alanine aminotransferase increased	27 (52.9)
Palmar-plantar erythrodysaesthesia syndrome	27 (52.9)
Nausea	26 (51.0)
Stomatitis	26 (51.0)
Blood amylase increased	26 (51.0)
Haemoglobin decreased	25 (49.0)
Face oedema	24 (47.1)
Nasopharyngitis	24 (47.1)
Hypothyroidism	23 (45.1)
Oedema peripheral	21 (41.2)
Malaise	20 (39.2)
Blood alkaline phosphatase increased	19 (37.3)
Blood albumin decreased	18 (35.3)
Epistaxis	17 (33.3)
Vomiting	16 (31.4)
Blood bilirubin increased	16 (31.4)
Anaemia	15 (29.4)
Blood phosphorus decreased	14 (27.5)
Eyelid oedema	13 (25.5)
Headache	13 (25.5)
Cheilitis	12 (23.5)
Dyspepsia	12 (23.5)
Blood calcium decreased	12 (23.5)
Back pain	12 (23.5)
Constipation	11 (21.6)
Cough	11 (21.6)
Protein total decreased	11 (21.6)

Twenty eight subjects (54.9%) experienced serious adverse events. All serious adverse events reported in this study are summarized in Table S5. One subject died during this study, and the cause of death was tumor progression and renal cell carcinoma (RCC), which was considered to be unrelated to study treatment.

Table S5. Serious Adverse Events[Number of Subjects (%)]

MedDRA Preferred Term (version 11.1)	Total (N=51)
Platelet count decreased	5 (9.8)
Dehydration	5 (9.8)
Nausea	4 (7.8)
Anorexia	4 (7.8)
Vomiting	3 (5.9)
Fatigue	3 (5.9)
Aspartate aminotransferase increased	3 (5.9)
Anaemia	2 (3.9)
Atrial fibrillation	2 (3.9)
Hypothyroidism	2 (3.9)
Malaise	2 (3.9)
Alanine aminotransferase increased	2 (3.9)
Blood alkaline phosphatase increased	2 (3.9)
Neutrophil count decreased	2 (3.9)
White blood cell count decreased	2 (3.9)
Myocardial infarction	1 (2.0)
Sick sinus syndrome	1 (2.0)
Thyroiditis	1 (2.0)
Anal fistula	1 (2.0)
Anal ulcer	1 (2.0)
Ascites	1 (2.0)
Diarrhoea	1 (2.0)
Gastrointestinal obstruction	1 (2.0)
Melaena	1 (2.0)
Upper gastrointestinal haemorrhage	1 (2.0)
Pyrexia	1 (2.0)
Bile duct stone	1 (2.0)
Cholecystitis	1 (2.0)
Hepatic function abnormal	1 (2.0)
Hyperbilirubinaemia	1 (2.0)
Sepsis	1 (2.0)
Blood bilirubin increased	1 (2.0)
Ejection fraction decreased	1 (2.0)
Hyperamylasaemia	1 (2.0)
Hypercalcaemia	1 (2.0)
Hypomagnesaemia	1 (2.0)
Hyponatraemia	1 (2.0)
Neoplasm progression	1 (2.0)
Headache	1 (2.0)
Proteinuria	1 (2.0)
Renal failure acute	1 (2.0)
Renal impairment	1 (2.0)
Cough	1 (2.0)
Dyspnoea	1 (2.0)
Haemothorax	1 (2.0)
Hypoxia	1 (2.0)
Interstitial lung disease	1 (2.0)
Pleural effusion	1 (2.0)
Pulmonary oedema	1 (2.0)
Drug eruption	1 (2.0)
Hypertension	1 (2.0)

Fifty-one (100%) subjects experienced Grade ≥3 adverse events. The most common Grade ≥3 adverse events (≥20%) included platelet count decreased, neutrophil count decreased, lipase increased, lymphocyte count decreased, and fatigue. The majority of these adverse events were considered treatment-related.

When summarized by treatment cycles, the overall incidences of Grade ≥3 adverse events were 65.8% to 84.3% (Cycle 1: 84.3%, Cycle 2: 74.4%, Cycle 3: 65.8%, Cycle 4: 77.1%), that did not show clear increase in frequency over time. The incidence of Grade ≥3 adverse events by MedDRA preferred term revealed a gradual increased incidence of diarrhoea (Cycle 1: 0%, Cycle 2: 2.3%, Cycle 3: 2.6%, Cycle 4: 5.7%) and palmar-plantar erythrodysaesthesia syndrome (Cycle 1: 0%, Cycle 2: 7.0%, Cycle 3: 7.9%, Cycle 4: 11.4%) over time.

Forty-six subjects (90.2%) required dose schedule modification (i.e., dosing interruption and/or dose reduction) due to an adverse event. The most common adverse events which led to dose schedule modification included platelet count decreased (26 subjects, 51.0%), neutrophil count decreased (23 subjects, 45.1%), white blood cell count decreased (15 subjects, 29.4%), fatigue (13 subjects, 25.5%), and palmar-plantar erythrodysaesthesia syndrome (11 subjects, 21.6%). Most of the adverse events led to dose schedule modification were well-managed with or without standard medical therapy.

Discontinuation due to an adverse event was reported in 15 subjects (29.4%). Adverse events leading to discontinuation of the study treatment are listed in Table S6.

Table S6. Adverse Events Leading to Discontinuation of the Study Treatment

Sex	Age (years)	Dose (mg/day)	MedDRA Preferred Term (version 11.1)	Causality	Outcome
Male	65	25	Ejection fraction decreased	Related	Not recovered
Female	60	25	Stomach discomfort	Related	Not recovered
Female	69	25	Malaise	Related	Not recovered
Female	76	37.5	Ejection fraction decreased	Related	Not recovered
Male	70	50	Atrial fibrillation	Related	Not recovered
			Thyroiditis	Related	Not recovered
Female	35	50	Forced expiratory volume decreased	Related	Not recovered
			Dyspnoea	Related	Recovered
			Hypoxia	Related	Recovered
			Pleural effusion	Related	Recovered
			Respiratory gas exchange disorder	Related	Not recovered
Female	34	37.5	Neoplasm progression	Not related	Death
Male	73	50	Hypertension	Related	Recovered
Male	62	25	Blood calcium increased	Related	Not recovered
Male	58	50	Chills	Related	Recovered
			Fatigue	Related	Recovered
			Pyrexia	Related	Recovered
Male	73	25	Hypothyroidism	Related	Not recovered
Male	58	25	Anaemia	Not related	Not recovered
Female	69	25	Fatigue	Related	Not recovered
Male	77	37.5	Interstitial lung disease	Related	Recovered
Male	76	50	Anorexia	Related	Not recovered
			Hypertension	Related	Not recovered

Hypertension and pyrexia were reported in more than half of the subjects, and those events led to the study discontinuation of 3 subjects (hypertension in 2 subjects; pyrexia in 1 subject); no significant adverse change was found in pulse rate and body weight. ECG QT corrected interval prolonged was experienced by 2 subjects (3.9%); however, both of the events were neither serious nor clinically significant and resolved without dose modification or discontinuation. The number of subjects who experienced left ventricular ejection fraction decreased did not increase over time. Two subjects experienced ejection fraction decreased as adverse events which led to discontinuation, 1 of which was serious, but abated after discontinuation of treatment.

CONCLUSIONS:

- SU-011248 had antitumor activity with an ORR of 48.0% in those subjects with metastatic RCC who had not had any prior systemic treatment, and with an ORR of 46.2% in those subjects who had previously been treated with one cytokine-based systemic therapy regimen.

- The AE profile of SU-011248 at 50-mg daily on a 4-weeks on/2-weeks off schedule was generally tolerable and manageable in both advanced-stage RCC subject populations.

- The median plasma trough concentrations of total drug reached therapeutically effective levels estimated from the nonclinical study results (>50 ng/mL) on Day 14 of Cycle 1 in both subject populations, and these levels were sustained during the subsequent treatment period without further accumulation of SU-011248 and SU-012662.

- There was no clear relationship between changes in pharmacodynamic markers, such as plasma VEGF and sVEGFR2 levels, and the best overall response.

- Subjects' HRQOL trended lower on treatment with SU-011248 and recovered during the off-treatment period.

- Median overall survival was 143.4 weeks in the first-line treatment population and 141.0 weeks in the pretreated population.