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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Sutent®/ Sunitinib malate/SU011248

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Sunitinib is approved in the USA for gastrointestinal stromal tumor after disease progression or intolerance to imatinib mesylate, and advanced renal cell carcinoma.

NCT NO.: NCT00092001

PROTOCOL NO.: A6181040

PROTOCOL TITLE: A Phase 2 Efficacy and Safety Study of SU011248 in Patients with Metastatic Non-Small Cell Lung Cancer

Study Centers: Italy, 1 center; Spain, 2 centers; United States of America, 7 centers

Study Initiation and Completion Dates: 18 January 2005 to 06 September 2006

Phase of Development: Phase 2

Study Objectives:

Primary:

To determine the antitumor efficacy of single-agent sunitinib malate at a dose of 50 mg orally once daily for 4 consecutive weeks repeated every 6 weeks, or 37.5 mg once daily continuously (4 week cycles), in subjects having metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of a platinum-based regimen and who had received ≤2 prior chemotherapy regimens.

Secondary:

- To assess duration of response (DR)
- To assess progression-free survival (PFS)
- To assess overall survival (OS)
- To evaluate the safety and tolerability of sunitinib malate

- To evaluate sunitinib malate and SU012662 plasma trough concentrations (C_{trough}) and to correlate C_{trough} with efficacy and safety parameters

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

METHODS

Study Design: This was a 2-cohort, open-label, multicenter, Phase 2 clinical study evaluating the efficacy and safety of single-agent sunitinib malate in subjects with advanced or metastatic NSCLC after failure of combination chemotherapy containing a platinum agent. Subjects could receive ≤2 prior chemotherapy regimens. Two cohorts with different dosing regimens of sunitinib malate were assessed.

Cohort 1 (Schedule 4/2; 4 weeks of daily treatment with sunitinib malate 50 mg followed by 2 weeks off treatment; 6-week cycles):

- The target sample size was 60 subjects. Using Simon's 2-stage Minimax design, if ≥2 subjects with objective tumor responses were observed in the first 39 treated subjects, then enrollment was to be expanded by 21 additional subjects in Stage 2, for a total of 60 treated subjects. After completing 9 cycles of sunitinib malate, subjects deriving clinical benefit could continue to receive sunitinib malate through participation in a separate protocol.

Cohort 2 (sunitinib malate at a starting dose of 37.5 mg/day in repeated 4-week cycles [continuous dosing]):

- If >5 subjects with objective tumor responses were observed in Cohort 1, then 44 subjects would be enrolled in a single-stage design. Alternatively, if ≤5 subjects with objective tumor responses were observed in Cohort 1, then Simon's 2-stage Minimax design was to be used for Cohort 2, where the target sample size was 29 subjects in Stage 1. If ≥2 subjects with objective tumor responses were observed in the first 29 treated subjects, then enrollment would be expanded by 15 additional subjects in Stage 2, for a total of 44 treated subjects. Up to 13 cycles could be administered in the absence of any withdrawal criteria.

This report presents results from Cohort 1. Results from Cohort 2 will be reported separately.

The study included a screening visit (within 21 days of study start), visits on Days 1, 14 and 28 of Cycle 1, Days 1 and 28 of Cycles 2 to 9, an end of study visit and a 28-day post-treatment follow-up visit. Subjects were also followed for survival.

Tumor assessments were made at screening and Day 28 of Cycles 1 to 4, 6 and 8, and end of treatment (if not performed during the preceding 6 weeks). Tumor assessments were also repeated to confirm a partial or complete response (≥4 weeks after the initial documentation of the response).

Number of Subjects (Planned and Analyzed): The target sample size was 60 subjects; subsequently 64 subjects were enrolled and 63 were treated.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥18 years with histologically proven NSCLC (Stage IV, recurrent disease or locally advanced [Stage IIIB]) not amenable to surgery, radiation, or combined modality therapy, with evidence of progressive disease within 6 months of the most recent systemic anticancer therapy were included in the study. Subjects were excluded if they had major surgery, thoracic radiation therapy or hemoptysis <4 weeks prior to study start, uncontrolled hypertension, previous treatment with anti-angiogenesis agents, specific cardiovascular or thromboembolic events <12 months prior to the study, any history of depressed left ventricular ejection fraction to below the lower limit of normal, any second malignancy (excluding adequately treated basal or squamous cell skin cancer, or in situ carcinoma of the cervix uteri) within 5 years of study start, history of brain metastases, spinal cord compression or carcinomatous meningitis or evidence of brain or leptomeningeal disease, any severe or acute chronic medical or psychiatric condition.

Study Treatment: Subjects received repeated 6-week cycles of 4 weeks treatment with a sunitinib malate 50 mg capsule daily, followed by 2 weeks off treatment, for a total of 9 cycles.

Sunitinib malate dose was adjusted according to individual subject tolerance.

Efficacy Evaluations:

Primary: The objective response rate (ORR); defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) relative to the total population of subjects who enrolled in the study with the correct histological cancer type, who had a baseline assessment of disease and received ≥1 dose of study medication.

Secondary: The DR, PFS, OS and the probability of survival at 1 year.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Blood samples for determination of C_{trough} for sunitinib malate and its active metabolite (SU012662) were obtained predose and analyzed using a validated method.

Plasma for assessment of soluble proteins was collected predose.

Blood samples were collected (PAXgene tube) for RNA expression profiling in peripheral blood cells with the aim of exploring the potential relationship with efficacy variables.

Tumor paraffin blocks (or at least five 4-micron slides prepared from the paraffin block) could be optionally provided for analyses of markers that may be associated with tumor proliferation or angiogenesis.

Safety Evaluations: Adverse events (AEs; at all visits) and laboratory evaluations (hematology and chemistry [at all visits; except chemistry was not evaluated on Day 28

during Cycles 5 to 9]; coagulation [prothrombin time], urinalysis and pregnancy test [at screening]), physical examination (at screening, Day 1 of all cycles, end of treatment and follow-up), vital signs (at screening, Days 1 and 28 of all cycles, end of treatment and follow-up) and electrocardiograms (at screening, Day 28 of Cycle 1 and end of treatment were carried out.

Statistical Methods: The intention-to-treat population (ITT; subjects who received ≥1 sunitinib malate dose) was used for the efficacy and safety analyses. The study was designed to test the null hypothesis that the true objective tumor response rate was ≤5% versus the alternative hypothesis that the true objective tumor response rate was ≥15%. The primary endpoint, ORR, was calculated and a 2-sided 95% confidence interval (CI) for ORR was provided using the exact method based on the F-distribution.

Time-to-event endpoints (PFS, DR and OS) were analyzed using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and a 2-sided 95% CI for each median were provided. DR was calculated only for the subgroup of subjects with a confirmed objective tumor response. The 1-year survival rate was estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log (-log [1-year survival rate]) was calculated using a normal approximation and then back transformed to give a CI for the 1-year survival rate itself.

Descriptive statistics were used to summarize all subject characteristics, diagnoses, treatment administration, efficacy endpoints, safety parameters, pharmacokinetic variables and cancer biomarkers. Relationships between baseline subject characteristics, pharmacokinetic parameters, or cancer biomarkers and outcome variables were explored using regression models or other appropriate techniques.

For sunitinib malate, SU012662 and total drug (sunitinib malate + SU012662), individual values and descriptive statistics (n, mean, standard deviation, coefficient of variation [CV], median, minimum and maximum) for C_{trough} were presented by Day and Cycle.

The results of biomarker studies were reported descriptively and in relation to clinical response and pharmacokinetic endpoints. Linear regression, t-test and analysis of variance (ANOVA) statistical methods were used to investigate correlations of biomarker levels with sunitinib malate concentrations and anti-tumor efficacy.

Analysis of gene expression profiling data was ongoing at the time of this report.

Adverse Events were coded according to the Medical Dictionary for Regulatory Activities, and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

RESULTS

Subject Disposition and Demography: The target sample size was 60 subjects, subsequently 64 were enrolled and 63 treated (Table 1). Two subjects (3.2%) completed 9 cycles per protocol. In total, 41 subjects (65.1%) discontinued due to lack of efficacy,

18 subjects (28.6%) discontinued due to AEs and 2 subjects (3.2%) withdrew consent. Subject disposition is summarized by cycle in Table 2.

Demographic and baseline characteristics are summarized in Table 3. Most subjects were white (85.7%), male (65.1%), and <65 years of age (69.8%), and approximately half had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 at baseline (55.6%). Fifty subjects (79.4%) either smoked or had previously smoked.

Table 1. Disposition - ITT

	Sunitinib malate N = 63
	n (%)
Treated	63 (100)
Completed[a]	2 (3.2)
Discontinued	61 (96.8)
Consent withdrawn	2 (3.2)
AEs	18 (28.6)
Lack of efficacy (disease progression)	41 (65.1)

[a] Subjects who completed the study were eligible to continue receiving treatment under a separate continuation protocol.

Table 2. Disposition by Cycle - ITT

Cycle	**Number of Subjects**		
	Treated	**Completed**	**Discontinued**
1	63	42	21
2	42	24	18
3	24	13	11
4	13	7	6
5	7	6	1
6	6	4	2
7	4	4	0
8	4	2	2
9	2	2	2[a]

[a] Subjects who completed the study were eligible to continue receiving treatment under a separate continuation protocol.

Table 3. Demography - ITT

	Sunitinib malate N = 63
Race [n (%)]	
White	54 (85.7)
Black	8 (12.7)
Not specified	1 (1.6)
Age (years)	
Mean (SD)	60.1 (10.4)
Range	33-86
<65	44 (69.8)
≥65	19 (30.2)
Sex [n (%)]	
Male	41 (65.1)
Female	22 (34.9)
Weight (kg)	
Mean (SD)	75.8 (15.8)
Range	42-115
ECOG performance status [n (%)]	
0	28 (44.4)
1	35 (55.6)
Smoking history [n (%)]	
Never smoked	10 (15.9)
Current smoker	10 (15.9)
Previous smoker	40 (63.5)
Unknown	3 (4.8)

ECOG = Eastern Cooperative Oncology Group

Table 4. Malignancy History - ITT

	Sunitinib malate N = 63
Histology [n, (%)]	
Adenocarcinoma	40 (63.5)
Squamous cell carcinoma	14 (22.2)
Bronchioloalveolar	2 (3.2)
Large cell carcinoma	2 (3.2)
Other	5 (7.9)
Number of metastatic sites [n, (%)]	
0	1 (1.6)
1	15 (23.8)
2	14 (22.2)
3	17 (27.0)
>3	16 (25.4)
Tumor, Node, Metastasis disease stage	
IV	57 (90.5)
IIIB	6 (9.5)
Number of prior systemic regimens	
1	25 (39.7)
2	30 (47.6)
3	6 (9.5)
4	2 (3.2)
Number of prior chemotherapy regimens	
1	37 (58.7)
2	23 (36.5)
3	3 (4.8)
Number of prior treatments with EGFR inhibitors[a]	
0	42 (66.7)
1	19 (30.2)
2	2 (3.2)
Prior treatments	
Platinum agent	59 (93.7)
Carboplatin	42 (66.7)
Gemcitabine	34 (54.0)
Paclitaxel	24 (38.1)
Cisplatin	19 (30.2)
Docetaxel	19 (30.2)
Erlotinib	12 (19.0)
Gefitinib	10 (15.9)
Pemetrexed	6 (9.5)
Irinotecan	3 (4.8)
Vinorelbine	2 (3.2)
Cetuximab	2 (3.2)
Etoposide	2 (3.2)
Bortezomib	2 (3.2)
Other	1 (1.6)
Previous surgery [n, (%)]	49 (77.8)
Previous radiotherapy [n, (%)]	27 (42.9)
Metastatic sites at screening	
Primary tumor	59 (93.7)
Lymph nodes	39 (61.9)
Lung	38 (60.3)
Local recurrence	38 (60.3)

Bone	24 (38.1)
Pleural effusion	15 (23.8)
Liver	13 (20.6)
Soft tissue	11 (17.5)
Adrenal gland	7 (11.1)
Skin metastases	5 (7.9)
Visceral organs	5 (7.9)
Peritoneal metastases	1 (1.6)
Other metastases	9 (14.3)

[a] The following drugs are defined as EGFR inhibitors: Iressa®, Tarceva®, Erbitux®, cetuximab, erlotinib and gefitinib.

Efficacy Results:

Seven subjects achieved PR. The ORR was 11.1% (7/63 subjects) with a 95% CI of 4.6 to 21.6% (Table 5). Based on Simon's 2-stage Minimax design, the null hypothesis that the true ORR was ≤5% was rejected with $\alpha = 0.10$. Objective responses were observed for 5/40 subjects (12.5%) with adenocarcinoma, 1/14 subjects (7.1%) with squamous cell carcinoma, and 1 subject with an unspecified histology.

Table 6 summarizes the time−to−event endpoints. Thirteen subjects (20.6%) did not experience progression or die due to any cause during the study. The median PFS was 12.0 weeks (95% CI: 10.0 to 16.1 weeks). In total, 24 subjects (38.1%) did not experience progression during the study and the median TTP was 15.1 weeks (95% CI: 11.3 to 18.3 weeks). Ten subjects (15.9%) were alive as of the date of the last known contact. The median OS was 23.4 weeks (95% CI: 17.0 to 28.3 weeks). The overall 1 year survival rate was 20.2% (95% CI: 10.0 to 30.4%).

Table 5. Overall Tumor Response

Number of Subjects (%)	**Sunitinib malate N = 63**
Measurable disease at baseline	63 (100.0)
Complete response	0
Partial response	7 (11.1)
Stable response	18 (28.6)
Progressive disease	18 (28.6)
Not evaluable	9 (14.3)
Missing	6 (9.5)
Overall response rate (CR + PR)	7 (11.1)
95% exact CI[a], %	(4.6, 21.6)

[a] 2-sided CI was calculated from a method based on the F distribution

CR = Complete response; PR = Partial response; CI = Confidence interval

Table 6. Summary of Time−to−Event Endpoints

	Number (%) Events[a]	Sunitinib malate N = 63 Median[b] (Weeks)	95% CI[b]
Progression-free survival	50 (79.4)	12.0	10.0, 16.1
Duration of response	4 (6.3)	21.2	12.1, not determined
Overall survival	53 (84.1)	23.4	17.0, 28.3

[a] For DR, only subjects who had a confirmed objective tumor response were counted; for OS, subjects who did not have an event were censored at the date they were last known to be alive

[b] For PFS, OS and DR analysis was based on the Kaplan-Meier estimate

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Median C_{trough}, measured at steady-state after 14 days of treatment, for sunitinib malate, SU012662 and total drug (sunitinib malate + SU012662) ranged from 54 to 68 ng/mL (14 to 53% CV), 21 to 28 ng/mL (51 to 67% CV) and 83 to 91 ng/mL (11 to 48% CV), respectively. The median total drug C_{trough} values were <5 ng/ml (ranging from 4.46 to 4.48 ng/ml) after 2 weeks off treatment. Total drug C_{trough} values were consistent for repeated cycles; no accumulation was observed.

Safety Results:

Adverse Events

Sixty-two subjects (98.4%) reported AEs, and 55 subjects (87.3%) reported AEs considered related to treatment (Table 7). In general, the most common events were consistent with conditions associated with advanced NSCLC and with the known toxicities of sunitinib malate. Common toxicities were generally constitutional (fatigue [38 subjects, 60.3%], dyspnea [22 subjects, 34.9%], anorexia [19 subjects, 30.2%], cough [16 subjects, 25.4%], headache [15 subjects, 23.8%], mucosal inflammation [13 subjects, 20.6%] and asthenia [10 subjects, 15.9%]) or gastrointestinal (nausea [28 subjects, 44.4%], diarrhea [21 subjects, 33.3%], vomiting [21 subjects, 33.3%], dysgeusia [17 subjects, 27.0%], stomatitis [15 subjects, 23.8%] and constipation [13 subjects, 20.6%]); other common AEs were back pain [11 subjects, 17.5%], oral pain [10 subjects, 15.9%], disease progression [13 subjects, 20.6%] and peripheral edema [10 subjects, 15.9%]. Disease progression was only reported as an AE when progression of a subject's malignancy had a fatal outcome. With the exceptions of dyspnea, cough, headache, constipation, back pain and peripheral edema, these common events were most often considered treatment-related.

Nineteen subjects (30.2%) died on-study (within 28 days of their last dose of sunitinib malate), and 34 subjects (54.0%) died during follow-up (>28 days after the last dose of sunitinib malate). Most on-study deaths (13/19; 20.6%) were considered related to progression of underlying cancer; the remaining 6/19 subjects (9.5%) died from cerebral hemorrhage, cerebrovascular accident, disseminated intravascular coagulation, hemorrhage, pneumothorax and pulmonary hemorrhage, 1 subject (1.6%) each, respectively; all considered treatment-related with the exception of cerebrovascular accident and hemorrhage. Of the 34 subjects (54.0%) who died during follow-up, 33 subjects (52.4%) died as result of progression of underlying disease, and 1 subject (1.6%) was crushed by a tractor.

Serious (S)AEs reported by more than 1 subject are summarized in Table 8. Thirty-seven subjects (58.7%) reported a total of 67 SAEs, including 10 subjects (15.9%) who reported 19 treatment-related SAEs. Treatment-related SAEs reported by more than 1 subject were dehydration (3 subjects), nausea (2 subjects) and vomiting (2 subjects). Only 1 subject reported an SAE (diarrhea) more than once which was considered related to treatment.

For the AE summary data, the number of subjects with AEs that led to discontinuation included some subjects who discontinued due to lack of efficacy as all AEs for which the "action taken" was "drug permanently withdrawn" were included. Therefore, the number of subjects with AEs that led to discontinuation in the AE summary data is higher than in the disposition summary data. The most commonly reported AEs which led to discontinuation were fatigue (4 subjects), asthenia (3 subjects), diarrhea (2 subjects) and vomiting (2 subjects).

In total, 22 subjects (34.9%) discontinued due to AEs: 8 subjects (12.7%) discontinued due to AEs considered related to study treatment; 4 subjects (6.3%) discontinued due to AEs related to both the study treatment and underlying disease; 12 subjects (19.0%) discontinued due to AEs related to the underlying disease; and 3 subjects (4.8%) discontinued due to AEs not considered related to study treatment or the underlying disease. Adverse events which led to the action "drug permanently withdrawn" and were reported by >1 subject were disease progression (5 subjects) and diarrhea (3 subjects); all considered related to study treatment.

Table 7. Most commonly reported AEs (≥15% of Subjects) – ITT

Preferred Term	Sunitinib malate N = 63			
	AEs		Treatment-related AEs	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any AE	62 (98.4)	1002	55 (87.3)	467
Fatigue	38 (60.3)	79	27 (42.9)	58
Nausea	28 (44.4)	47	23 (36.5)	37
Dyspnea	22 (34.9)	27	0	0
Diarrhea	21 (33.3)	39	17 (27.0)	30
Vomiting	21 (33.3)	31	13 (20.6)	17
Anorexia	19 (30.2)	27	15 (23.8)	21
Dysgeusia	17 (27.0)	20	16 (25.4)	19
Cough	16 (25.4)	17	0	0
Stomatitis	15 (23.8)	19	14 (22.2)	18
Headache	15 (23.8)	25	3 (4.8)	3
Constipation	13 (20.6)	16	5 (7.9)	6
Disease progression	13 (20.6)	13	0	0
Mucosal inflammation	13 (20.6)	17	11 (17.5)	15
Back pain	11 (17.5)	18	2 (3.2)	2
Oral pain	10 (15.9)	15	9 (14.3)	14
Asthenia	10 (15.9)	13	6 (9.5)	7
Edema peripheral	10 (15.9)	16	4 (6.3)	9

AE = adverse event

Table 8. Summary of Serious Adverse Events

Preferred Term	Sunitinib malate N = 63			
	SAEs[a]		Treatment-related SAEs	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any SAE	37 (58.7)	67	10 (15.9)	19
Disease progression	13 (20.6)	13	0	0
Dehydration	3 (4.8)	3	3 (4.8)	3
Hemoptysis	3 (4.8)	3	1 (1.6)	1
Deep vein thrombosis	3 (4.8)	3	0	0
Nausea	2 (3.2)	2	2 (3.2)	2
Vomiting	2 (3.2)	2	2 (3.2)	2
Fatigue	2 (3.2)	2	1 (1.6)	1
Pleural effusion	2 (3.2)	3	0	0
Cerebrovascular accident	2 (3.2)	2	0	0
Dyspnea	2 (3.2)	2	0	0
Respiratory failure	2 (3.2)	2	0	0

[a] Reported by more than 1 subject

AE = adverse event

Vital Signs

Overall, 24 subjects (38.1%) experienced hypertension, defined as systolic BP >150 mmHg and/or diastolic BP >100 mmHg, at least once during the study; however, no subjects were reported to experience systolic BP >200 mmHg and/or diastolic BP >110 mmHg. Seven subjects (11.1%) reported hypertension as an AE, of which 3 subjects (4.8%) experienced Grade 3 hypertension (none experienced Grade 4). No subjects discontinued the study because of hypertension.

Laboratory Evaluations

There was considerable variability between subjects for most hematology tests. In general, there was a decrease between baseline and end of Cycle 1 for the mean absolute neutrophil count (ANC), eosinophil, lymphocyte, monocyte, platelet and white blood cell (WBC) levels, but not for mean levels of hematocrit, hemoglobin, red blood cells (RBC) and basophils. There was a continual decrease after Cycle 1 in the mean ANC, but not for mean levels of RBC, eosinophils, basophils, hematocrit, hemoglobin, lymphocytes, monocytes, and WBC. There was considerable variability between subjects for most serum chemistry tests, but there was no evidence of a clinically significant change in the mean chemistry values with time after dosing for any chemistry variable, with the possible exceptions of indirect and total bilirubin, creatinine kinase and lactate dehydrogenase (LDH), which appeared to peak at Day 28 during Cycles 1 to 4; given the extremely high variance at those time points, these peaks most likely represent a small number of subjects with extreme values, rather than a systematic change across a large number of subjects. In addition, there appeared to be a peak

for bicarbonate during Cycle 4 on Day 28, which returned to below baseline in subsequent cycles. Electrocardiograms

There was no evidence of a clinically significant change in mean or median QTc interval during or after Cycle 1 of treatment and there were no QTc results assessed as Grade ≥ 3 or as clinically significant.

CONCLUSIONS: Treatment with sunitinib malate at a starting dose of 50 mg daily for 4 consecutive weeks in repeated 6-week cycles demonstrated promising single-agent activity in subjects with metastatic NSCLC. A clinically relevant ORR of 11.1% was observed.

In this study, the AE profile of sunitinib malate was consistent with the known toxicity profile of sunitinib malate.