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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00372775

PROTOCOL NO.: A6181092

PROTOCOL TITLE: A Phase 2 Efficacy and Safety Study of SU-011248 in Patients With Non-Small Cell Lung Cancer and Brain Metastases

Study Centers: The study was conducted at 5 centers in the United States, 2 centers in Spain, 4 centers in Italy, and 4 centers in France.

Study Initiation and Completion Dates: 13 March 2007 to 10 December 2009

Phase of Development: Phase 2

Study Objectives: The primary objective was to evaluate the efficacy of sunitinib in subjects with non-small cell lung cancer (NSCLC) and brain metastases, previously treated with whole brain radiotherapy (WBRT) and up to 1-2 prior systemic therapies.

Secondary objectives were:

- To evaluate the intracranial antitumor activity of sunitinib in subjects with NSCLC and brain metastases, previously treated with WBRT and up to 1-2 prior systemic therapies, and having measurable brain disease;
- To evaluate the safety and tolerability of sunitinib administered in a continuous dose treatment regimen;
- To assess patient-reported outcomes (PRO);
- To evaluate sunitinib and SU-012662 trough concentrations (C_{trough}) and to correlate these plasma concentrations with efficacy and safety parameters; and
- To explore the relationships of cancer biomarkers with clinical outcomes.

METHODS

Study Design:

This study was an open-label, single-arm, Phase 2 clinical study evaluating the efficacy and safety of single-agent sunitinib 37.5 mg on a continuous daily dosing schedule in subjects with metastatic NSCLC to the brain. Subjects must have previously received WBRT and may have also received up to 1-2 prior systemic therapies. A total of 60 subjects were planned to be treated.

Subjects were to receive sunitinib for 13 cycles (approximately 1 year) or until a subject withdrawal criterion was met, whichever was earlier. Follow-up survival information, including post-study anticancer treatment, was to be collected by clinic visits or telephone contact every 2 months until death, or 1 year from the last subject's first dose of study treatment, whichever was earlier. Subjects still receiving benefit from treatment, in the investigator's opinion, were to be offered continued access to sunitinib through participation in a separate extension protocol.

Number of Subjects (Planned and Analyzed): A total of 60 subjects were planned to be enrolled. A total of 64 subjects were randomized and treated.

Diagnosis and Main Criteria for Inclusion: Subjects with histologically or cytologically confirmed NSCLC, radiologically proven metastatic NSCLC to the brain, and up to 1-2 previous systemic therapies were eligible to participate in the study. Additionally, subjects must have been ≥18 years of age, had adequate organ function, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study Treatment: Sunitinib malate (sunitinib) was administered as an oral capsule at a starting dose of 37.5 mg once daily (3 x 12.5-mg capsules) given continuously (1 cycle = 4 weeks) for up to 13 cycles. Sunitinib dose was to be titrated on an individual basis depending on tolerability. Subjects experiencing Grade ≤1 nonhematological or Grade ≤2 hematological toxicity attributed to sunitinib within the first 8 weeks of treatment could have their dose escalated to 50 mg daily. Subjects experiencing sunitinib-related toxicity requiring dose interruption or dose reduction could reduce to 25 mg daily. Subsequent dose adjustments were permitted based on outcome.

Efficacy Evaluations: The primary efficacy parameter was progression free survival (PFS) based on the investigator's response assessments for subjects with NSCLC and brain metastases in the intent-to-treat (ITT) population (all subjects who were enrolled in the study and who received at least 1 dose of study drug).

The secondary efficacy parameters were:

- Time to tumor progression (TTP; overall, intracranial);
- Time to neurological progression;
- Objective response rate (overall; ORR);

- Intracranial ORR (in those subjects who recurred following WBRT);
- Duration of response (DR; overall, intracranial);
- Overall survival (OS); and
- One-year survival.

For all tumor assessments, response and progression were defined by the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0).

Other Efficacy Evaluations: Other evaluations included PROs and pharmacogenomic (PGx) evaluations.

PROs as measured by Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Lung Symptom Index (FLSI) and the FACT/NCCN Brain Symptom Index (FBrSI).

PGx evaluations included collection of tumor samples for specified molecular profiling analyses. In subjects who consented, formalin-fixed, paraffin-embedded blocks collected at the time of the most recent recurrence and/or at the time of initial diagnosis were requested, although collection at any time was acceptable.

PGx evaluations included collection of blood samples for specified genotyping.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Blood samples for the measurement of SU-011248 plasma concentrations were to be collected before dosing on Day 1 (predose) of Cycles 2 to 4. All trough samples were to be collected approximately 24 hours after the last dose and before the next dose.

Safety Evaluations: Safety evaluations included adverse events (AEs) from the first day of treatment to 28 days after the last dose of study drug; clinical laboratory tests (hematology and biochemistry); electrocardiogram (ECG; performed at screening and Day 1 Cycle 2); vital signs; and ECOG performance status.

Statistical Methods: The primary endpoint of PFS was analyzed in the ITT population using the Kaplan-Meier method.

Time-to-event endpoints (ie, PFS, TTP [overall and intracranial], time to neurological progression, DR [duration of response; overall and intracranial] and overall survival) were analyzed using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and a 2-sided 95% confidence interval (CI) for each median are provided. The 1-year survival probability was estimated using the Kaplan-Meier method and a 2-sided 95% CI (and 90% CI for PFS) for the log (-log [1-year survival]) was calculated using a normal approximation and then back transformed to give a CI for the 1-year survival.

The number and percent of subjects achieving an objective response (overall and intracranial) at any time during the study were summarized along with the corresponding exact 2-sided 95% CI based on the F-distribution.

Summaries of AEs and of other safety data are presented in tabular and/or graphical format and summarized descriptively.

RESULTS

Subject Disposition and Demography:

A summary of subject evaluation groups is provided in Table 1.

A total of 66 subjects were assigned to study treatment, and 64 subjects were treated. Two subjects were randomized, but not treated: Subject 10011001 chose alternate treatment before being treated and Subject 10321006 had global deterioration of health status before being treated. The ITT and safety population included 64 subjects who were analyzed for efficacy, and 45 (70.3%) subjects provided PRO data. A total of 3 (4.7%) subjects completed the study, and 61 (95.3%) subjects discontinued from the study.

Table 1. Subject Evaluation Groups (All Subjects)

	Sunitinib n (%)
Number of subjects	
Assigned to study treatment	66
Treated (ITT/safety population)[a]	64
Completed	3 (4.7)
Discontinued	61 (95.3)
Analyzed for efficacy	
PFS/TTP/TNP/OS	64 (100.0)
BOR – overall	61 (95.3)
BOR – intracranial	23 (35.9)
DR – overall	1 (1.6)
DR – intracranial	1 (1.6)
Analyzed for PRO[b]	45 (70.3)
Analyzed for safety	
Adverse events	64 (100.0)
Laboratory data	61 (95.3)

Abbreviations: ITT=Intent-To-Treat; n=number of subjects; PFS=progression-free survival; TTP=time to tumor progression; TNP=time to neurological progression; OS=overall survival; BOR=best overall response; DR=duration of response; PRO=patient-reported outcome

[a] The ITT population included all subjects enrolled in the study who received at least 1 dose of study drug.

[b] The ITT population of subjects with post-baseline and nonmissing baseline PRO data.

A summary of the demographic and baseline characteristics is provided in Table 2.

Table 2. Demographic and Baseline Characteristics (Intent-To-Treat Population)

Variable	Sunitinib (N=64)
Gender, n	
Male	39 (60.9)
Female	25 (39.1)
Age (years), n (%)	
<18	0
18-44	4 (6.3)
45-64	40 (62.5)
≥65	20 (31.3)
Age (years)	
Mean (SD)	59.3 (9.3)
Median	60.5
Range	35.0-77.0
Race, n (%)	
White	60 (93.8)
Other	4 (6.3)
Weight (kg)	
Mean (SD)	70.9 (13.9)
Median	71.5
Range	45.3-103.4
ECOG Performance Status, n (%)	
0	35 (54.7)
1	28 (43.8)
2	1 (1.6)
Smoker, n (%)	
Smoker	9 (14.1)
Ex-smoker	20 (31.3)
Never smoked	35 (54.7)

Abbreviations: N, n=number of subjects; SD=standard deviation; ECOG=Eastern Cooperative Oncology Group

Efficacy Results:

The primary endpoint for this study was PFS based on disease progression and death as assessed by the investigators. A total of 52/64 (81.3%) subjects experienced disease progression or died during the study; 36 (56.3%) had objective disease progression and 16 (25.0%) died without objective disease progression. The median PFS was 9.4 weeks (90% CI: 7.5-13.1 weeks). For the subset of subjects who had progressive disease (PD) (intracranial or extracranial) as best response to WBRT, 7/9 (77.8%) experienced disease progression or died during the study; 5 (55.6%) had objective disease progression and 2 (22.2%) died without objective disease progression. The median PFS was 12.5 weeks (95% CI: 9.8, 24.1). For the subset of subjects who did not have PD as best response to WBRT, 45/55 (81.8%) experienced disease progression or died during the study; 31 (56.4%) had objective disease progression and 14 (25.5%) died without objective disease progression. The median PFS was 7.7 weeks (95% CI: 6.4, 13.1).

Secondary endpoints included TTP (overall, intracranial, and neurological), ORR, intracranial ORR, DR, OS, and 1-year survival). The median overall TTP was 15.1 weeks

(95% CI: 8.4, 15.8). The median intracranial TTP was 15.4 weeks (95% CI: 12.1, 24.8). For best overall objective response (complete response [CR] + partial response [PR]) by RECIST, 61 (95.3%) subjects with measurable disease at baseline were evaluated. One subject had an objective response (PR) for an ORR of 1.6% (95% CI: 0.0, 8.8) with a DR of 32.1 weeks. A total of 23 (35.9%) subjects with measurable intracranial disease at baseline were evaluated for best intracranial objective response (CR + PR) by the World Health Organization (WHO). One subject had an objective intracranial response (PR) for an intracranial ORR of 4.3% (95% CI: 0.1, 21.9) with a DR of 8.3. A total of 54 (84.4%) subjects died and 10 (15.6%) subjects were in follow-up as of the data cutoff date. The median OS was 5.8 months (95% CI: 3.1, 8.2).

Pharmacokinetic, Pharmacokinetic/Pharmacodynamic, and Pharmacogenomic Results:

Pharmacokinetic Results

Following continuous daily dosing of sunitinib, mean C_{trough} on Day 1 of Cycles 2, 3, and 4 for SU-011248, its metabolite, and total drug ranged from 35.5 ng/mL to 43.7 ng/mL, 21.8 ng/mL to 28.7 ng/mL, and 57.3 ng/mL to 72.4 ng/mL, respectively.

Dose-corrected (reference dose: 37.5 mg) mean C_{trough} values for SU-011248, its metabolite, and total drug at steady state (Day 1 of Cycles 2, 3, and 4) ranged from 46.3 ng/mL to 51.1 ng/mL, 28.5 ng/mL to 33.9 ng/mL, and 74.7 ng/mL to 84.7 ng/mL, respectively.

Pharmacokinetic/Pharmacodynamic Results

For the AE of nausea, the incidence was similar between the 2 pharmacokinetic (PK) subpopulations (above or below the median total drug concentration on Day 1 Cycle 2) regardless of the AE grade. The incidence of diarrhea was very low (approximately 11% for all grades and <6% for Grades 1 and 2), appearing only in the below the median PK subpopulations. The scatter plot of change in absolute neutrophil counts from baseline vs total drug C_{trough} did not show any consistent trend, suggesting that no correlation between the extent of change in neutrophil count and total drug C_{trough} could be established.

The rate (%) appeared to be higher for stable disease (SD) and lower for progressive disease (PD) in the above the median PK subpopulation for both total body and intracranial solid tumors. Consistent with the tumor response findings, the Kaplan-Meier curves for PFS and OS showed some degree of differentiation between the 2 PK subpopulations, indicating better PFS and OS in the above the medical PK subpopulation.

Pharmacogenomic Results

Only 4 tumor samples were collected; therefore, no formal statistical analyses were performed or will be performed on these samples.

The objective of the coded genetic analysis of blood samples was to explore the genetic contribution of KIT, fms-related-like tyrosine kinase-3 (FLT3), and colony-stimulating factor 1 receptor (CSF1R) polymorphisms to sunitinib-related myelosuppression and fatigue, as subjects with lowered levels of KIT, FLT3, and CSF1R gene products due to germline

deoxyribonucleic acid (DNA) variations might be at increased risk for sunitinib toxicity. Of the 46 genotyped samples collected in the study, a total of 44 samples were used in the AE-related analysis. Because of the small sample size that resulted in a lack of power for statistical testing, no formal statistical test for the association between endpoints and genetic variation as measured by single nucleotide polymorphisms (SNPs) is presented, and data were summarized descriptively.

Safety Results:

A summary of all-causality treatment-emergent AEs by preferred term in at least 5% of subjects is provided in Table 3. A summary of discontinuations due to AEs is provided in Table 4. A summary of subject deaths is provided in Table 5. A summary of serious adverse events (SAEs) is provided in Table 6.

Table 3. Descending Order of Frequency of All Causality Treatment-Emergent Adverse Events by Preferred Term Reported in at Least 5% of Subjects

	Sunitinib (N=64)	
MedDRA Preferred Term	Maximum CTCAE Grade 3/4 n (%)	Total n (%)
Any adverse event	26 (40.6)	63 (98.4)
Fatigue	5 (7.8)	24 (37.5)
Constipation	2 (3.1)	16 (25.0)
Decreased appetite	2 (3.1)	16 (25.0)
Cough	0	15 (23.4)
Nausea	2 (3.1)	14 (21.9)
Disease progression	0	13 (20.3)
Dyspnea	6 (9.4)	13 (20.3)
Diarrhea	0	12 (18.8)
Hypertension	3 (4.7)	12 (18.8)
Vomiting	1 (1.6)	12 (18.8)
Asthenia	2 (3.1)	11 (17.2)
Mucosal inflammation	1 (1.6)	11 (17.2)
Thrombocytopenia	2 (3.1)	9 (14.1)
Arthralgia	0	8 (12.5)
Abdominal pain upper	0	7 (10.9)
Abdominal pain	1 (1.6)	6 (9.4)
Dyspepsia	0	6 (9.4)
Hypokalemia	4 (6.3)	6 (9.4)
Pyrexia	0	6 (9.4)
Anemia	1 (1.6)	5 (7.8)
Bone pain	1 (1.6)	5 (7.8)
Chest pain	1 (1.6)	5 (7.8)
Dry skin	0	5 (7.8)
General physical health deterioration	4 (6.3)	5 (7.8)
Hemoptysis	2 (3.1)	5 (7.8)
Headache	0	5 (7.8)
Neutropenia	2 (3.1)	5 (7.8)
Pain	2 (3.1)	5 (7.8)
Rash	0	5 (7.8)
Dysguesia	0	4 (6.3)
Platelet count decreased	1 (1.6)	4 (6.3)
Stomatitis	0	4 (6.3)

Abbreviations: N/n=number of subjects; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities

Table 4. Discontinuations Due to Adverse Events

System Organ Class	MedDRA Preferred Term	Sunitinib (N=64)	
		All Causality n (%)	Treatment Related n (%)
Any AE		29 (45.3)	8 (12.5)
Blood and Lymphatic System Disorders	Anemia	1 (1.6)	0
Cardiac Disorders	Pericarditis	1 (1.6)	0
General Disorders and Administrative Site Conditions	Disease progression	6 (9.4)	0
	General physical health deterioration	4 (6.3)	2 (3.1)
	Pyrexia	1 (1.6)	0
Injury, Poisoning, and Procedural Complications	Fracture	1 (1.6)	0
Investigations	Platelet count decreased	1 (1.6)	1 (1.6)
	Pulmonary function test decreased	1 (1.6)	0
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal chest pain	1 (1.6)	0
Nervous System Disorders	Cerebellar syndrome	1 (1.6)	0
	Facial palsy	1 (1.6)	0
	Headache	1 (1.6)	0
	Hemiapraxia	1 (1.6)	0
	Hemiparesis	1 (1.6)	0
	Mental impairment	1 (1.6)	0
	Tremor	1 (1.6)	0
Psychiatric Disorders	Intentional self injury	1 (1.6)	0
Renal and Urinary Disorders	Renal failure	1 (1.6)	1 (1.6)
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea	2 (3.1)	0
	Hemoptysis	1 (1.6)	1 (1.6)
	Pulmonary embolism	2 (3.1)	2 (3.1)
	Respiratory failure	2 (3.1)	0
Skin and Subcutaneous Tissue Disorders	Rash	1 (1.6)	1 (1.6)

Abbreviations: N/n=number of subjects; MedDRA=Medical Dictionary for Regulatory Activities; AE=adverse event

Table 5. Subject Deaths

Subject Status	Sunitinib (N=64)
Subjects who died	54 (84.4)
Subjects who died while on study[a]	19 (29.7)
Disease under study[b]	16 (84.2)
Other[c]	3 (15.8)
Subjects who died during follow-up[d]	35 (54.7)
Disease under study[b]	32 (91.4)
Unknown	3 (8.6)

Abbreviation: N = number of subjects
[a] On-study deaths were those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
[b] Subjects may have had more than 1 cause of death specified.
[c] Other reasons included suicide, worsening of respiratory function, and chronic obstructive pulmonary disease.
[d] Follow-up deaths were those that occurred more than 28 days after the last dose of study drug.

Table 6. Serious Adverse Events

	Sunitinib (N=64)	
MedDRA Preferred Term	All Causality n (%)	Treatment Related n (%)
Any SAE	34 (53.1)	7 (10.9)
Disease progression	13 (20.3)	0
Respiratory failure	3 (4.7)	0
Convulsion	2 (3.1)	0
Epilepsy	2 (3.1)	0
General physical health deterioration	2 (3.1)	1 (1.6)
Hemoptysis	2 (3.1)	2 (3.1)
Pulmonary embolism	2 (3.1)	2 (3.1)
Pyrexia	2 (3.1)	0
Vomiting	2 (3.1)	2 (3.1)
Abdominal pain	1 (1.6)	1 (1.6)
Apthous stomatitis	1 (1.6)	1 (1.6)
Bone pain	1 (1.6)	0
Cardiac tamponade	1 (1.6)	0
Cerebellar syndrome	1 (1.6)	0
Cerebral ischemia	1 (1.6)	0
Constipation	1 (1.6)	1 (1.6)
Duodenal ulcer	1 (1.6)	0
Dysphagia	1 (1.6)	1 (1.6)
Febrile neutropenia	1 (1.6)	0
Fracture	1 (1.6)	0
Glossodynia	1 (1.6)	1 (1.6)
Infection	1 (1.6)	0
Intentional self injury	1 (1.6)	0
Jaundice	1 (1.6)	1 (1.6)
Lung infection	1 (1.6)	0
Musculoskeletal chest pain	1 (1.6)	0
Neck pain	1 (1.6)	0
Oral pain	1 (1.6)	1 (1.6)
Oropharyngeal pain	1 (1.6)	1 (1.6)
Pericarditis	1 (1.6)	0
Pneumonitis	1 (1.6)	0
Pulmonary function test decreased	1 (1.6)	0
Pyelonephritis	1 (1.6)	1 (1.6)
Thrombocytopenia	1 (1.6)	1 (1.6)
Tremor	1 (1.6)	0

Abbreviations: N/n=number of subjects; SAE=serious adverse event; MedDRA=Medical Dictionary for Regulatory Activities

A total of 4 subjects had a Grade 4 hematology laboratory abnormality during the study (1 with Grade 4 hemoglobin, 1 with Grade 4 platelets, 1 with Grade 4 white blood cells, and 1 with Grade 4 absolute lymphocytes). A total of 3 subjects had a Grade 4 chemistry laboratory abnormality during the study (1 with Grade 4 hypokalemia, 1 with Grade 4 hypocalcemia, and 1 with Grade 4 hypermagnesemia).

A total of 3 (5.5%) subjects had a systolic blood pressure with at least a 40 mm Hg increase from baseline during the study. A total of 2 (3.6%) subjects had a diastolic blood pressure

with at least a 30 mm Hg increase from baseline during the study. Both of these cases were reported as AEs, although there were no hypertension-associated complications.

There was 1 subject with a clinically significant abnormal ECG finding during the study (left ventricular hypertrophy with repolarization). Two subjects had Grade 3 or higher QTcF intervals (changes from baseline of 83 and 163 msec). These QTcF intervals were not reported as AEs and did not lead to dose reduction or study discontinuation.

CONCLUSIONS:

- Sunitinib 37.5 mg on a continuous daily dosing schedule did not meet the pre-specified efficacy criterion in this study, with a median PFS of 9.4 weeks (90% CI: 7.5-13.1 weeks) in 64 NSCLC subjects with brain metastases previously treated with WBRT and up to 2 prior systemic therapies.

- Intracranial antitumor activity was observed, with an intracranial ORR of 4.3% and an intracranial TTP of 15.4 weeks.

- The overall AE and laboratory profile in this subject population was generally tolerable and clinically manageable, without any cases of intracranial hemorrhage.

- Subjects' quality of life was maintained during sunitinib treatment, as overall symptom burden remained stable during sunitinib treatment.

- Mean trough concentrations for sunitinib and its metabolite in NSCLC subjects with brain metastases were consistent with those previously reported in subjects with gastrointestinal stromal tumors (GIST) and metastatic renal cell carcinoma (MRCC).

- There was a trend towards improved PFS and OS in the PK subpopulation with higher Cycle 2 Day 1 trough concentrations, supporting a greater likelihood of antitumor activity with higher plasma exposures to sunitinib and its active metabolite.