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

PROTOCOL NO.: A6181037

PROTOCOL TITLE: A SU011248 Expanded Access Protocol for Systemic Therapy of Patients With Metastatic Renal Cell Carcinoma who are Ineligible for Participation in Other SU011248 Protocols but may Derive Benefit From Treatment With SU011248

Study Centers: The study was conducted at a total of 124 centers; 18 in the United States, 9 in the United Kingdom, 8 in Italy, 7 each in Germany, Canada, France, and Spain, 5 in Brazil, 4 each in Australia, and Mexico, 3 each in Belgium, Switzerland, and India , 2 each in Argentina, the Czech Republic, Greece, the Netherlands, Romania, the Russian Federation, Sweden and Poland, 1 each in Austria, Bulgaria, Colombia, Croatia, Ecuador, Egypt, Finland, Hong Kong, Ireland, Israel, the Republic of Korea, Lebanon, Malaysia, Panama, Peru, the Philippines, Portugal, Singapore, Slovakia, Taiwan, Thailand, Turkey, and Venezuela.

Study Initiation Date and Final Completion Dates: 27 June 2005 to 29 November 2011

Phase of Development: Not applicable

Study Objectives:
Primary objective: To provide access to sunitinib treatment for subjects with metastatic renal cell carcinoma (RCC) given all of the following conditions were met:

- Subjects were ineligible for participation in ongoing sunitinib clinical studies (if any Phase 1, 2 or 3 sunitinibprotocols for subjects having RCC were open to enrollment at the institution) except for those subjects who received interferon (IFN)-α therapy in Protocol A6181034 and either had radiographic documentation of disease progression or were IFN-α intolerant.

- Subjects had the potential to derive clinical benefit from treatment with sunitinib based on the judgment of the Investigator.

Secondary objectives: Assessment of

- the safety and tolerability profile of sunitinib.

- the antitumor efficacy of single agent sunitinib given orally at a dose of 50 mg in subjects with metastatic RCC.

METHODS

Study Design: This study was an open-label "expanded access" protocol for subjects with metastatic RCC with the disease status and treatment background described in the study objectives. The primary objective, to provide access to sunitinib, was done without formal hypothesis testing. Assessments and procedures including post-study and follow-up are outlined in Table 1. Subjects could continue to receive treatment until they experienced progressive disease or unacceptable toxicity.

Table 1. Schedule of Events

Protocol Activities and Forms to Be Completed	Screen	Cycle 1			Cycle 2		Cycle ≥ 3	End of Treatment/ Withdrawal	Post-Treatment	Survival Follow-up
	Days –45 to 1	Day 1 -1/+0	Day 14[a] -3/+3	Day 28 or End of Dosing –3/+3	Day 1 -1/+0	Day 28 or End of Dosing –3/+3	Day 1[b] -1/0			
Informed consent	X									
Documented ineligible for open sunitinib studies[c]										
Medical history	X									
Physical examination, ECOG performance status	X	(X) 3			X		X	X	(X)[d]	
Laboratory Studies										
Pregnancy test[e]	X									
Hematology	X	(X) 3	(X)	X	X	X	X	X	(X) [d]	
Biochemistry	X	(X) 3		X	X	X	X	X	(X) [d]	
Other Assessments										
12-lead ECG[f]		X		X				X	(X)	
Disease assessment	X					X Standard of Care	X Standard of Care			
Adverse events[g]	X	X	X	X	X	X	X	X	X	
Concomitant medications/ treatments[h]	X	X	X	X	X	X	X	X	X	
Study treatment		X→	→	→X	X→	→X	→X			
Study drug compliance				X		X	X	X		
Post-study survival status[i]										X[i]

(X) - if applicable; X→ - start and continue treatment; → - continue treatment; →X - stop treatment.
ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IEC = Independent ethics committee; IRB = Institutional review board; RCC = renal cell cancer.

a. Cycle 1, Day 14 Visit: This visit could be handled by telephone contact unless otherwise required on a country basis. If a site visit was done, hematology and biochemistry could be performed.
b. The schedule was modified with Amendment 7; until that time a Day 28 visit was also required on Cycles ≥3.
c. Ineligibility for other sunitinib Protocols: If any Phase 1, 2 or 3 protocols for subjects having metastatic RCC were open to enrollment at the institution, subjects were required to be declared ineligible before being considered for participation in this study.
d. Physical Examination/Hematology/Biochemistry: Required at the post-treatment assessment if withdrawal was due to toxicity. Physical examination/Hematology/Biochemistry at Day 1, Cycle 1 were not required if acceptable assessments had been done within 7 days of Day 1, unless

Table 1. Schedule of Events

additional tests were clinically indicated. ECOG performance status was also assessed.

e. Pregnancy Test: Required within 21 days before the first dose of sunitinib for women of reproductive potential. Pregnancy tests could also be repeated as per request of IEC/IRBs or if required by local regulations (eg, Austria).

f. 12-lead ECG: Three 12-lead ECGs were performed at least 2 minutes apart at baseline (acceptable if done during the screening period within 7 days of Day 1), Cycle 1, Day 28, and at End of Treatment/Study Withdrawal to determine the mean QTc interval. The ECGs were to be performed in the morning and be time matched (±1 hour). If the mean QTc was prolonged (>500 msec), then the ECGs were to be over read by a cardiologist at the clinical site for confirmation. Additional ECGs were performed as clinically indicated.

g. Adverse Events: Subjects were required to be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. Serious adverse events were monitored and reported as described. Serious adverse events were monitored and reported from the time that the subject provide informed consent. The assessment scheduled for Day 14 of the first cycle could be accomplished through telephone contact unless otherwise required on a country basis.

h. Concomitant Medications/Treatments: Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment, during the study, and up to 28 days post the last dose of study treatment.

i. Post Study Survival Status: Follow-up survival information was collected for all subjects by clinic visit or telephone contact every 2 months for up to 2 years from the date of first dose of sunitinib until 30 September 2008; at that time it was determined that the study had met survival-related endpoints and long-term follow-up was discontinued.

Number of Subjects (Planned and Analyzed): Due to the nature of this study, no inferential analyses were planned, and no hypotheses were tested. The number of subjects to be enrolled was not predetermined. Up to 5000 subjects could have been enrolled. A total of 4577 were enrolled in the study, of which 4543 received at least 1 dose of sunitinib and qualified for the intent-to-treat (ITT) population. The study enrolled a total of 4543 subjects: 650 in Italy, 575 in the United Kingdom, 361 in France, 320 in the United States, 307 in Canada, 301 in Germany, 224 in Poland, 142 in Austria, 123 in Brazil, 116 in Belgium, 100 in Republic of Korea, 97 in Spain, 94 in Netherlands, 74 in India, 71 in Croatia, 63 each in Mexico and Argentina, 59 in Hungary, 58 in Russia, 52 in Romania, 51 in Turkey, 50 in Czech Republic, 41 in Slovakia, 35 in Malaysia, 34 each in Israel and Egypt, 31 in Serbia, 29 in Singapore, 27 each in Sweden and Australia, 25 each in Bulgaria and Greece, 24 each in Colombia and Lebanon, 22 in Taiwan, 21 each in Peru and Slovenia, 20 each in Finland and Panama, 19 in Switzerland, 16 in Thailand, 14 each in Ecuador and Hong Kong, 13 each in Philippines and Venezuela, 9 in Norway, 8 each in Portugal and Bosnia And Herzegovina, 7 in Ireland, 6 in Chile and 5 in Missing group.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, 18 years or older with renal cell carcinoma that was not amendable to standard therapy with curative intent. Exclusion Criteria included current treatment in another therapeutic clinical trial.

Study Treatment: Sunitinib was supplied in hard gelatin capsules in 12.5 mg, 25 mg and 50 mg dose strengths and was self-administered orally, as a single agent, once daily in the morning. Bottles containing the correct capsule strength were dispensed to the subject at the start of each treatment cycle. Sunitinib was administered on Schedule 4/2 (4 weeks of daily dosing followed by 2 weeks off-treatment in repeated 6-week cycles). The starting dose was 50 mg daily (treatment of some subjects was started at 37.5 mg daily). However, if there was evidence of tumor growth or if the subject's clinical condition worsened during the 2 weeks off sunitinib, the Investigator could change the dosing regimen to continuous daily dosing. Cycles changed from 6 to 4 weeks in duration on the continuous daily dosing (CDD) regimen. Subjects were to complete at least 2 cycles on Schedule 4/2 and to complete their current cycle of treatment before starting the CDD regimen. For subjects on the CDD regimen, the typical starting dose was 37.5 mg once daily. However, the initial starting dose could be modified within a pre-specified range based on the subject's prior experience on Schedule 4/2. The sunitinib dose was titrated on an individual basis depending on tolerability. Subjects experiencing only grade ≤1 non-hematologic or grade ≤2 hematologic toxicity attributed to sunitinib within the first 8 weeks of treatment at 37.5 mg daily could be escalated to 50 mg daily dosing.

Efficacy Endpoints:

Primary endpoint:

To provide access to sunitinib treatment for subjects with metastatic RCC according to conditions described in the protocol without formal hypothesis testing.

Secondary endpoints:

- Safety profile of sunitinib.
- Overall survival (OS).
- Time to tumor progression (TTP).
- Progression free survival (PFS).
- Objective response rate (ORR).

Safety Evaluations*:* Adverse events, laboratory tests, and vital signs were assessed throughout the study.

Baseline tumor-related signs and symptoms were recorded as adverse events during the trial if they worsened in severity or increased in frequency.

Statistical Methods: No inferential efficacy analyses or formal statistical hypotheses were tested. However, ORR, TTP, PFS, OS and DR were assessed.

The study population for all analyses was defined as all subjects enrolled in the study who received at least 1 dose of study medication (ITT population), with the exception that subjects with non- Response Evaluation Criteria in Solid Tumors (RECIST) tumor measurements or other data integrity issues were excluded from the efficacy analyses based on tumor response data. All RECIST response assessments provided by the Investigator were included in the analyses; the Investigator was to follow each subject for 28 days after the last dose.

ORR was defined as the percent of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST, relative to the total analysis population. Confirmed responses were those that persisted on repeat imaging study ≥4 weeks after initial documentation of response. The ORR was provided along with the corresponding exact 95% 2-sided confidence interval (CI) using standard methods based on the binomial distribution. The summaries of best ORR were provided for all subjects and for subsets of subjects based on various prognostic factors.

Time to tumor progression (TTP) was defined as the time from date of first dose of study medication to first documentation of objective tumor progression.

Progression free survival (PFS) was defined as the time from first dose of study medication to first documentation of objective tumor progression, or to death due to any cause, whichever occurred first. For subjects who discontinued or were lost to follow-up before tumor progression or death, PFS data were censored at the date of the last tumor evaluation demonstrating lack of response.

Overall survival (OS) was defined as the time from date of first dose of study medication to first documentation of death due to any cause. Survival data were censored at the date the subject was last known to be alive.

Duration of response (DR) was defined as the time from first observation of an objective response that is subsequently confirmed to first documentation of objective tumor progression, or to death due to any cause, whichever occurred first. For subjects who discontinued or were lost to follow-up before tumor progression or death, DR data were censored at the date of the last tumor evaluation demonstrating lack of response.

Estimates of TTP, PFS, OS and DR were performed using Kaplan-Meier product limit algorithms. Subject disposition, subject demography and other baseline characteristics, and drug administration were summarized by descriptive statistics. Safety analyses were summarized descriptively.

RESULTS

Subject Disposition and Demography: Table 2 is an overall summary of subject disposition. Overall in the ITT population, 240 subjects (5.3%) completed the study according to the end-of-study case report form, and 4298 subjects (94.6%) discontinued treatment.

Table 2. Overall Summary of Subject Disposition for All Subjects

Variable	sunitinib
Enrolled Subjects	4577
Intent-to-Treat Subjects [N][a]	4543
Completed Subjects	240
Subjects Assigned to and who received 37.5 mg sunitinib [n (%)]	70 (1.5)
Subjects who had a dose reduction [n (%)][b]	2241
Dose reduction to 37.5 mg	1525 (33.6)
Dose reduction to 25 mg	690 (15.2)
Dose reduction to 15 mg	1 (0.0)
Dose reduction to 12.5 mg	25 (0.6)

% = (n/N)*100
N = total number of subjects; n = number of subjects with defined criteria.
a. The Intent-to-Treat (ITT) population includes all subjects enrolled in the study that receive at least 1 dose of study medication.
b. For subjects who had multiple dose reductions, the lowest dose the subject reduced to is summarized.

Demographic and baseline characteristics are summarized in Table 3.

Table 3. Summary of Demographic and Baseline Characteristics (Safety Population)

Variable Statistic or Category	Sunitinib (N=4543)
Age (Years)	
N	4543
Mean (standard deviation)	59.2 (10.8)
Median (range)	59 (19.0, 89.0)
<65 years [n (%)]	3058 (67.3)
≥65 years [n (%)]	1485 (32.7)
Sex [n (%)]	
Male	3364 (74.0)
Female	1179 (26.0)
Race [n (%)]	
White	3673 (80.8)
Black	29 (0.6)
Asian	346 (7.6)
Other	441 (9.7)
Missing	54 (1.2)
Prior Nephrectomy [n (%)]	
Yes	4044 (89.0)
No	300 (6.6)
Missing	199 (4.4)
ECOG Performance Status [n (%)]	
0	1868 (41.1)
1	1949 (42.9)
2	547 (12.0)
3	80 (1.8)
4	7 (0.2)
Missing	92 (2.0)
Prior Cytokines [n (%)]	
Yes	3096 (68.1)
No	1447 (31.9)

ECOG = Eastern Cooperative Oncology Group; IFN = Interferon; LDH = Lactic dehydrogenase; N = total number of subjects; n = number of subjects with defined criteria.

Efficacy Results: In the efficacy analyses, 660 subjects had an objective tumor response; the overall ORR was 15.6% (95% CI of 14.6% to 16.8%). A total of 1893 subjects (44.9% overall) had a best response of stable disease (SD) for 3 months or more. Time-to-event endpoints are summarized in Table 4.

Table 4. Summary of Time-to-Event Endpoints (ITT Population)

	Total (N=4543[a])		
Variable	**Number (%) Events[b]**	**Median[c] (Weeks)**	**95% CI[c] (Weeks)**
TTP	2178 (51.6)	50.9	48.3 to 53.0
DR	374 (56.7[d])	82.1	74.4 to 87.6
OS	2551 (56.2)	81.1	76.0 to 84.7
PFS	2724 (64.6)	40.7	38.0 to 43.3

DR = Duration of tumor response; N = total number of subjects; OS = Overall survival; PFS = Progression free survival; TTP = Time to tumor progression; RECIST = Response Evaluation Criteria in Solid Tumors.

a. For measurement based endpoints, 324 ITT subjects were excluded due to non-RECIST tumor assessments or data integrity issues.
b. Two thousand forty-one subjects who were not known to have progressive disease at the time the database was closed for analysis were censored on the date they were last known to be without disease progression; 1992 subjects who were not know to be dead at the time the database was closed for analysis were censored on the date they were last known to be alive.
c. Based on Kaplan-Meier estimates.
d. Percentage for DR is based on the 660 subjects with objective tumor responses.

The survival rate at 1 year was 62.5% (95% CI: 61.0% to 63.9%).

A summary of the best ORR as determined by the investigator is provided in Table 5.

Table 5. Summary of Best Overall Tumor Response (ITT Population[a])

Variable	**Sunitinib (N=4219)**
Best confirmed tumor response [n (%)]	
Complete Response	63 (1.5)
Partial Response	597 (14.2)
Stable Disease	2168 (51.4)
SD <3 months	275 (6.5)
SD ≥3 months	1893 (44.9)
Progressive Disease	525 (12.4)
Not assessed	250 (5.9)
Not evaluable	19 (0.5)
Missing	597 (14.2)
Objective Response (CR + PR) [n (%)]	660 (15.6)
95% Exact CI[b]	(14.6, 16.8)

CI = confidence interval; CR = complete response; ITT = intent to treat; N = total number of subjects; n = number of subjects with specified criteria; PR = Partial response; SD = Stable disease; RECIST = Response Evaluation Criteria in Solid Tumors.

a. 324 ITT subjects excluded due to non-RECIST tumor assessments or data integrity issues.
b. Using exact method based on binomial distribution.

Summaries of TTP are presented in Table 6. The overall median TTP was 50.9 weeks (95% CI: 48.3 to 53.0 weeks).

Table 6. Summary of Time to Tumor Progression (Weeks) (Intent-to-Treat Population)[a]

Variable	Sunitinib (N=4219)
Progression status [n (%)]	
Subject did not progress	2041 (48.4)
Subject observed to have progressed	2178 (51.6)
Time to progression (Weeks)	
Quartile (95% confidence interval)	
25%	24.0 (23.4, 24.9)
50% (median)	50.9 (48.3, 53.0)
75%	101.6 (95.9, 109.7)

% = (n/N)*100
N = total number of subjects; n = number of subjects meeting specified criteria; RECIST = Response Evaluation Criteria in Solid Tumors.
a. 324 intent-to-treat subjects were excluded due to non-RECIST tumor assessments or data integrity issues.

Summaries of DR are presented in Table 7. Among the 660 subjects with a confirmed tumor response to treatment (CR or PR), the median DR was 82.1 weeks (95% CI: 74.4 to 87.6 weeks).

Table 7. Summary of Duration of Tumor Response (Weeks) (Intent-to-Treat Population)[a]

Variable	Sunitinib (N=4219)
Total number of responders [N*]	660
Subjects with a response who have not progressed or died due to any cause[b]	286 (43.3)
Subjects with a response and subsequent progression or death due to any cause[b]	374 (56.7)
Duration of response (Weeks)	
Quartile (95% confidence interval)	
25%	42.4 (39.3, 49.0)
50% (median)	82.1 (74.4, 87.6)
75%	156.1 (133.4,182.3)

% = (n/N*)*100, where N* is the number of subjects with objective tumor response.
N = total number of subjects; RECIST = Response Evaluation Criteria in Solid Tumors.
a. 324 intent-to-treat subjects were excluded due to non-RECIST tumor assessments or data integrity issues.
b. Only deaths that occurred within 28 days of the last dose are counted as events. Disease progression was not restricted to the treatment + 28 day follow—up period.

Overall survival is summarized in weeks in Table 8.

Table 8. Summary of Overall Survival (Weeks) (Intent-to-Treat Population)

Variable	Sunitinib (N=4543)
Subject survival status	[n (%)]
Alive[a]	1992 (43.8)
Dead	2551 (56.2)
Survival Time (weeks)	
Quartile (95% confidence interval)	
25%	31.0 (29.1, 33.0)
50% (median)	81.1 (76.0, 84.7)
75%	292.6 (247.9,)
K-M estimates of survival probability (95% CI)	0.24 (0.21, 0.28)

% = (n/N)*100.
KM estimate of survival probability is the Kaplan-Meier estimate of the probability that an individual is alive past the last observed event time.
N = total number of subjects; n = no of subject with defined criteria.
a. Subjects who were not known to be dead at the time of analysis or on a selected cut-off date were censored on the date they were last known to be alive.

PFS is summarized in weeks in Table 9

Table 9. Summary of Progression-Free Survival (Weeks) (Intent-to-Treat Population)[a]

Variable	Sunitinib (N=4219)
Progression status	[n (%)]
Subject did not progress or die due to any cause[b]	1495 (35.4)
Subject observed to have progressed or died due to any cause[b]	2724 (64.6)
Progression-free survival time (weeks)	
Quartile (95% confidence interval)	
25%	17.7 (16.6, 19.0)
50% (Median)	40.7 (38.0, 43.3)
75%	85.6 (82.0, 92.4)
K-M estimates of survival probability (95% CI)	0.04 (0.03, 0.06)

% = (n/N)*100.
KM estimate of survival probability is the Kaplan-Meier estimate of the probability that an individual is progression-free past the last observed event time.
N = total number of subjects; n = no of subject with defined criteria; RECIST = Response Evaluation Criteria in Solid Tumors.
a. 324 intent-to-treat subjects were excluded due to non-RECIST tumor assessments or data integrity issues.
b. Only deaths that occurred within 28 days of the last dose are counted as events. Disease progression was not restricted to the treatment + 28 day follow-up period.

Safety Results: In the overall safety population (4543) a total of 4492 subjects (98.9%) experienced adverse events, and 4328 subjects (95.3%) experienced adverse events that were

considered related to the study drug. All-causality and treatment-related adverse events experienced by ≥5% subjects are summarized in Table 10.

Table 10. Incidence of All-Causality and Treatment-Related Adverse Events by ≥5% Subjects (Safety Population)

MedDRA Preferred Term	Sunitinib (N=4543)			
	All-Causality AEs		Treatment-Related AEs	
	Subjects n (%)	Events	Subjects n (%)	Events
Any Adverse Events	4492 (98.9)	112,295	4328 (95.3)	83,797
Diarrhea	2279 (50.2)	6348	2122 (46.7)	5885
Fatigue	2011 (44.3)	4766	1809 (39.8)	4170
Nausea	1822 (40.1)	3546	1629 (35.9)	3056
Decreased appetite	1618 (35.6)	2900	1398 (30.8)	2470
Vomiting	1499 (33.0)	2800	1250 (27.5)	2237
Mucosal inflammation	1347 (29.7)	3063	1332 (29.3)	3024
Stomatitis	1286 (28.3)	2963	1277 (28.1)	2942
Palmar-plantar erythrodysesthesia syndrome	1225 (27.0)	4073	1221 (26.9)	4045
Hypertension	1215 (26.7)	1932	1104 (24.3)	1748
Asthenia	1189 (26.2)	2784	1021 (22.5)	2412
Dysgeusia	1171 (25.8)	2034	1152 (25.4)	1999
Anemia	1094 (24.1)	2594	783 (17.2)	1710
Thrombocytopenia	1064 (23.4)	3047	1037 (22.8)	2981
Constipation	966 (21.3)	1475	641 (14.1)	956
Dyspepsia	924 (20.3)	1539	844 (18.6)	1398
Dyspnea	922 (20.3)	1447	327 (7.2)	442
Rash	840 (18.5)	1581	772 (17.0)	1455
Cough	805 (17.7)	1157	304 (6.7)	393
Headache	797 (17.5)	1243	521 (11.5)	769
Back pain	795 (17.5)	1226	253 (5.6)	347
Neutropenia	746 (16.4)	2593	736 (16.2)	2555
Pyrexia	730 (16.1)	968	324 (7.1)	388
Pain in extremity	727 (16.0)	1396	455 (10.0)	914
Edema peripheral	719 (15.8)	1079	421 (9.3)	606
Epistaxis	702 (15.5)	1084	616 (13.6)	919
Abdominal pain	679 (14.9)	1024	361 (7.9)	530
Yellow skin	598 (13.2)	994	593 (13.1)	986
Arthralgia	587 (12.9)	871	290 (6.4)	393
Hypothyroidism	540 (11.9)	593	516 (11.4)	566
Abdominal pain upper	533 (11.7)	833	423 (9.3)	660
Skin discoloration	494 (10.9)	768	491 (10.8)	762
Hair color changes	492 (10.8)	558	490 (10.8)	555
Dry skin	478 (10.5)	620	461 (10.1)	596
Leukopenia	459 (10.1)	1373	451 (9.9)	1333
Disease progression	424 (9.3)	431	3 (0.1)	4
Insomnia	385 (8.5)	468	210 (4.6)	248
Chest pain	379 (8.3)	489	117 (2.6)	140
Weight decreased	378 (8.3)	493	230 (5.1)	314
Myalgia	375 (8.3)	522	286 (6.3)	395
Dizziness	355 (7.8)	450	213 (4.7)	271
Alopecia	331 (7.3)	382	299 (6.6)	343

Table 10. Incidence of All-Causality and Treatment-Related Adverse Events by ≥5% Subjects (Safety Population)

MedDRA Preferred Term	Sunitinib (N=4543)			
	All-Causality AEs		Treatment-Related AEs	
	Subjects n (%)	Events	Subjects n (%)	Events
Blood creatinine increased	310 (6.8)	643	171 (3.8)	322
Oral pain	308 (6.8)	585	298 (6.6)	571
Face edema	292 (6.4)	500	253 (5.6)	423
Erythema	291 (6.4)	423	254 (5.6)	381
Musculoskeletal pain	288 (6.3)	397	95 (2.1)	108
Hemoptysis	287 (6.3)	419	153 (3.4)	212
Pain	285 (6.3)	353	118 (2.6)	142
Lacrimation increased	281 (6.2)	400	269 (5.9)	384
Pruritus	267 (5.9)	337	244 (5.4)	299
Dehydration	256 (5.6)	298	114 (2.5)	133
Bone pain	246 (5.4)	325	64 (1.4)	73
Dry mouth	243 (5.3)	285	231 (5.1)	272
Nasopharyngitis	241 (5.3)	322	53 (1.2)	56
Oropharyngeal pain	239 (5.3)	329	165 (3.6)	227
Urinary tract infection	232 (5.1)	304	61 (1.3)	71
Paresthesia	229 (5.0)	306	172 (3.8)	228
Glossodynia	228 (5.0)	445	222 (4.9)	439
Flatulence	228 (5.0)	313	197 (4.3)	272

SAE and AE results are not separated out in this table.
AE = Adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N= total number of subjects; n = number of subjects with an AE; SAE = Serious adverse events.

Treatment-emergent, all-causality adverse event data are summarized in Table 11.

Table 11. Treatment-Emergent Adverse Events (All Causality) Reported in ≥5% Subjects

MedDRA Preferred Term	Sunitinib (N=4543) n (%)
Any AEs	4492 (98.9)
Diarrhea	2279 (50.2)
Fatigue	2011 (44.3)
Nausea	1822 (40.1)
Decreased appetite	1618 (35.6)
Vomiting	1499 (33.0)
Mucosal inflammation	1347 (29.7)
Stomatitis	1286 (28.3)
Palmar-plantar erythrodysesthesia syndrome	1225 (27.0)
Hypertension	1215 (26.7)
Asthenia	1189 (26.2)
Dysgeusia	1171 (25.8)
Anemia	1094 (24.1)
Thrombocytopenia	1064 (23.4)
Constipation	966 (21.3)
Dyspepsia	924 (20.3)
Dyspnea	922 (20.3)
Rash	840 (18.5)
Cough	805 (17.7)
Headache	797 (17.5)
Back pain	795 (17.5)
Neutropenia	746 (16.4)
Pyrexia	730 (16.1)
Pain in extremity	727 (16.0)
Edema peripheral	719 (15.8)
Epistaxis	702 (15.5)
Abdominal pain	679 (14.9)
Yellow skin	598 (13.2)
Arthralgia	587 (12.9)
Hypothyroidism	540 (11.9)
Abdominal pain upper	533 (11.7)
Skin discoloration	494 (10.9)
Hair color changes	492 (10.8)
Dry skin	478 (10.5)
Leukopenia	459 (10.1)
Disease progression	424 (9.3)
Insomnia	385 (8.5)
Chest pain	379 (8.3)
Blood creatinine increased	378 (8.3)
Weight decreased	378 (8.3)
Myalgia	375 (8.3)
Dizziness	355 (7.8)
Alopecia	331 (7.3)
Oral pain	308 (6.8)
Face edema	292 (6.4)
Erythema	291 (6.4)
Musculoskeletal pain	288 (6.3)
Hemoptysis	287 (6.3)

Table 11. Treatment-Emergent Adverse Events (All Causality) Reported in ≥5% Subjects

MedDRA Preferred Term	Sunitinib (N=4543) n (%)
Pain	285 (6.3)
Lacrimation increased	281 (6.2)
Pruritus	267 (5.9)
Dehydration	256 (5.6)
Bone pain	246 (5.4)
Dry mouth	243 (5.3)
Nasopharyngitis	241 (5.3)
Oropharyngeal pain	239 (5.3)
Urinary tract infection	232 (5.1)
Paresthesia	229 (5.0)
Flatulence	228 (5.0)
Glossodynia	228 (5.0)

AE = Adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N= total number of subjects; n = number of subjects with an AE.

Serious adverse events: A total of 2237 subjects (49.2%) experienced SAEs, and 983 subjects (21.6%) experienced SAEs considered related to the study drug. All-causality and treatment-related serious adverse events experienced by ≥1% subjects are summarized in Table 12.

Table 12. Incidence of All-Causality and Treatment-Related Serious Adverse Events by ≥1% Subjects (Safety Population)

Preferred Term[a]	Sunitinib (N=4371)			
	All-Causality SAEs		Treatment-Related SAEs	
	Subjects n (%)	Events	Subjects n (%)	Events
Any Serious Adverse Events	2237 (49.2)	5739	983 (21.6)	2053
Disease progression	336 (7.4)	339	1 (<0.1)	1
Dyspnea	175 (3.9)	197	26 (0.6)	28
Vomiting	167 (3.7)	187	114 (2.5)	125
Dehydration	124 (2.7)	136	57 (1.3)	62
Anemia	122 (2.7)	145	51 (1.1)	58
General physical health deterioration	114 (2.5)	126	14 (0.3)	14
Asthenia	111 (2.4)	121	70 (1.5)	78
Pyrexia	111 (2.4)	115	36 (0.8)	36
Pleural effusion	108 (2.4)	128	11 (0.2)	12
Diarrhea	104 (2.3)	121	80 (1.8)	96
Pneumonia	104 (2.3)	109	15 (0.3)	15
Thrombocytopenia	102 (2.2)	120	96 (2.1)	113
Abdominal pain	98 (2.2)	109	23 (0.5)	26
Nausea	85 (1.9)	96	56 (1.2)	62
Fatigue	62 (1.4)	66	42 (0.9)	45
Renal failure	62 (1.4)	64	24 (0.5)	25
Pulmonary embolism	52 (1.1)	54	16 (0.4)	16
Hypertension	51 (1.1)	52	43 (0.9)	44
Confusional state	50 (1.1)	56	17 (0.4)	20
Hyponatremia	46 (1.0)	51	28 (0.6)	30

N = total number of subjects; n = number of subjects with SAE; SAE = serious adverse event.

a. Four subjects (<0.1%) experienced a total of 4 SAEs that were uncoded. Uncoded events were collapse, decrease of general status, deterioration, and suspected gastrointestinal bleeding with underlying renal cell carcinoma.

Discontinuations: A total of 1152 subjects (25.4%) experienced AEs that had an action taken recorded as permanent withdrawal from drug (including subjects who experienced AEs that were considered related to the study disease and were therefore considered to have discontinued the study because of disease progression).

Deaths: A total of 803 subjects (17.7%) died on study; note that because this count included non-treatment-emergent deaths and deaths that may have been reported only on the follow-up CRF (and not the adverse event CRF), it is higher than the number of grade 5 (death) adverse events. There were 717 subjects (15.8%) with grade 5 adverse events. Grade 5, all-causality adverse events are summarized in Table 13.

Table 13. Incidence of All Causality and Treatment-Related Grade 5 (Death) Adverse Events (Safety Population)

Preferred Term	Sunitinib (N=4543)	
	All-Causality Deaths	Treatment-Related Deaths
	Subjects n (%)	Subjects n (%)
Any grade 5 AE	717 (15.8)	80 (1.8)
Disease progression	344 (7.6)	1 (<0.1)
General physical health deterioration	60 (1.3)	3 (0.1)
Respiratory failure	25 (0.6)	3 (0.1)
Cerebral hemorrhage	15 (0.3)	6 (0.1)
Death	14 (0.3)	5 (0.1)
Renal failure	11 (0.2)	4 (0.1)
Pulmonary embolism	11 (0.2)	3 (0.1)
Myocardial infarction	11 (0.2)	3 (0.1)
Pneumonia	11 (0.2)	2 (<0.1)
Cardiac arrest	11 (0.2)	1 (<0.1)
Renal cell carcinoma	11 (0.2)	0 (0.0)
Cerebrovascular accident	10 (0.2)	1 (<0.1)
Acute respiratory failure	10 (0.2)	0 (0.0)
Cardiac failure	9 (0.2)	4 (0.1)
Multi-organ failure	7 (0.2)	2 (<0.1)
Renal failure acute	7 (0.2)	0 (0.0)
Sepsis	6 (0.1)	2 (<0.1)
Hemorrhage	6 (0.1)	2 (<0.1)
Dyspnea	6 (0.1)	1 (<0.1)
Metastases to central nervous system	6 (0.1)	0 (0.0)
Cardio-respiratory arrest	5 (0.1)	0 (0.0)
Metastatic renal cell carcinoma	5 (0.1)	0 (0.0)
Sudden death	4 (0.1)	1 (<0.1)
Hepatic failure	4 (0.1)	4 (0.1)
Septic shock	4 (0.1)	3 (0.1)
Pulmonary edema	4 (0.1)	2 (<0.1)
Hemoptysis	4 (0.1)	1 (<0.1)
Neoplasm progression	4 (0.1)	0 (0.0)
Pleural effusion	4 (0.1)	0 (0.0)
Renal cancer	4 (0.1)	0 (0.0)
Gastrointestinal hemorrhage	3 (0.1)	3 (0.1)
Pulmonary hemorrhage	3 (0.1)	1 (<0.1)
Cardiopulmonary failure	3 (0.1)	1 (<0.1)
Acute pulmonary edema	3 (0.1)	0 (0.0)
Brain edema	3 (0.1)	0 (0.0)
Condition aggravated	3 (0.1)	0 (0.0)
Intestinal perforation	2 (<0.1)	2 (<0.1)
Gastritis hemorrhagic	2 (<0.1)	2 (<0.1)
Cerebral hematoma	2 (<0.1)	2 (<0.1)
Acute myocardial infarction	2 (<0.1)	2 (<0.1)
Performance status decreased	2 (<0.1)	1 (<0.1)
Hypotension	2 (<0.1)	1 (<0.1)
Abdominal pain	2 (<0.1)	0 (0.0)
Bronchopneumonia	2 (<0.1)	0 (0.0)
Circulatory collapse	2 (<0.1)	0 (0.0)

Table 13. Incidence of All Causality and Treatment-Related Grade 5 (Death) Adverse Events (Safety Population)

Preferred Term	Sunitinib (N=4543)	
	All-Causality Deaths	Treatment-Related Deaths
	Subjects n (%)	Subjects n (%)
Disseminated intravascular coagulation	2 (<0.1)	0 (0.0)
Fatigue	2 (<0.1)	0 (0.0)
Hematemesis	2 (<0.1)	0 (0.0)
Hypoxia	2 (<0.1)	0 (0.0)
Liver disorder	2 (<0.1)	0 (0.0)
Pulmonary thrombosis	2 (<0.1)	0 (0.0)
Pyrexia	2 (<0.1)	0 (0.0)
Urosepsis	1 (<0.1)	1 (<0.1)
Tracheo-esophageal fistula	1 (<0.1)	1 (<0.1)
Thrombocytopenia	1 (<0.1)	1 (<0.1)
Shock	1 (<0.1)	1 (<0.1)
Rhabdomyolysis	1 (<0.1)	1 (<0.1)
Retroperitoneal abscess	1 (<0.1)	1 (<0.1)
Pulmonary congestion	1 (<0.1)	1 (<0.1)
Pneumocystis jiroveci pneumonia	1 (<0.1)	1 (<0.1)
Perinephric abscess	1 (<0.1)	1 (<0.1)
Nephritis	1 (<0.1)	1 (<0.1)
Necrotizing fasciitis	1 (<0.1)	1 (<0.1)
Myocarditis	1 (<0.1)	1 (<0.1)
Large intestine perforation	1 (<0.1)	1 (<0.1)
Ischemic stroke	1 (<0.1)	1 (<0.1)
Hemothorax	1 (<0.1)	1 (<0.1)
Hematochezia	1 (<0.1)	1 (<0.1)
Dehydration	1 (<0.1)	1 (<0.1)
Cytolytic hepatitis	1 (<0.1)	1 (<0.1)
Cerebral ischemia	1 (<0.1)	1 (<0.1)
Asthenia	1 (<0.1)	1 (<0.1)
Arterial rupture	1 (<0.1)	1 (<0.1)
Adrenal insufficiency	1 (<0.1)	1 (<0.1)
Accident	1 (<0.1)	0 (0.0)
Acute coronary syndrome	1 (<0.1)	0 (0.0)
Acute hepatic failure	1 (<0.1)	0 (0.0)
Acute respiratory distress syndrome	1 (<0.1)	0 (0.0)
Aortic aneurysm rupture	1 (<0.1)	0 (0.0)
Aortic dissection	1 (<0.1)	0 (0.0)
Cachexia	1 (<0.1)	0 (0.0)
Carbon monoxide poisoning	1 (<0.1)	0 (0.0)
Cardiac failure acute	1 (<0.1)	0 (0.0)
Cardiogenic shock	1 (<0.1)	0 (0.0)
Cardiovascular insufficiency	1 (<0.1)	0 (0.0)
Chronic obstructive pulmonary disease	1 (<0.1)	0 (0.0)
Coagulopathy	1 (<0.1)	0 (0.0)
Coma	1 (<0.1)	0 (0.0)
Deep vein thrombosis	1 (<0.1)	0 (0.0)
Depressed level of consciousness	1 (<0.1)	0 (0.0)
Fistula	1 (<0.1)	0 (0.0)

Table 13. Incidence of All Causality and Treatment-Related Grade 5 (Death) Adverse Events (Safety Population)

Preferred Term	Sunitinib (N=4543)	
	All-Causality Deaths	Treatment-Related Deaths
	Subjects n (%)	Subjects n (%)
Gastric cancer	1 (<0.1)	0 (0.0)
Gastric fistula	1 (<0.1)	0 (0.0)
Gastric hemorrhage	1 (<0.1)	0 (0.0)
Gastrointestinal perforation	1 (<0.1)	0 (0.0)
Hemolysis	1 (<0.1)	0 (0.0)
Hemorrhagic stroke	1 (<0.1)	0 (0.0)
Hepatorenal syndrome	1 (<0.1)	0 (0.0)
Hydropneumothorax	1 (<0.1)	0 (0.0)
Hyperbilirubinemia	1 (<0.1)	0 (0.0)
Hypercalcemia	1 (<0.1)	0 (0.0)
Hypertensive heart disease	1 (<0.1)	0 (0.0)
Hyponatremia	1 (<0.1)	0 (0.0)
Hypovolemic shock	1 (<0.1)	0 (0.0)
Ileus	1 (<0.1)	0 (0.0)
Ileus paralytic	1 (<0.1)	0 (0.0)
Infection	1 (<0.1)	0 (0.0)
Intentional overdose	1 (<0.1)	0 (0.0)
Intestinal obstruction	1 (<0.1)	0 (0.0)
Intracranial pressure increased	1 (<0.1)	0 (0.0)
Lung infiltration	1 (<0.1)	0 (0.0)
Malignant peritoneal neoplasm	1 (<0.1)	0 (0.0)
Meningitis	1 (<0.1)	0 (0.0)
Metastasis	1 (<0.1)	0 (0.0)
Myocardial ischemia	1 (<0.1)	0 (0.0)
Esophageal carcinoma	1 (<0.1)	0 (0.0)
Orthostatic hypotension	1 (<0.1)	0 (0.0)
Peritonitis bacterial	1 (<0.1)	0 (0.0)
Renal cancer metastatic	1 (<0.1)	0 (0.0)
Respiratory acidosis	1 (<0.1)	0 (0.0)
Respiratory disorder	1 (<0.1)	0 (0.0)
Staphylococcal sepsis	1 (<0.1)	0 (0.0)
Subileus	1 (<0.1)	0 (0.0)
Toxicity to various agents	1 (<0.1)	0 (0.0)
Tumour embolism	1 (<0.1)	0 (0.0)
Tumour hemorrhage	1 (<0.1)	0 (0.0)
Viral infection	1 (<0.1)	0 (0.0)

There were 2 uncoded grade 5 adverse events. The verbatim terms were "deterioration" and "suspected gastrointestinal bleeding with underlying renal cell carcinoma"; both were considered unrelated to treatment. These events are counted in the total row but not under individual preferred terms.
AE = adverse events; N = total number of subjects; n = number of subjects with specified criteria.

CONCLUSIONS: Access to sunitinib was provided to a substantial number of subjects who did not qualify for other sunitinib studies; 4543 subjects received sunitinib through this protocol, with treatment periods extending up to 6 years.

No unexpected types or frequencies of adverse events were identified in this expanded access trial.

The safety profile, including common adverse events and less common, more severe adverse events, was comparable to what has been observed with sunitinib before as indicated in the prescribers' information for SUTENT®.

Efficacy results (ORR, PFS, and OS) suggested that treatment with sunitinib malate resulted in clinical benefit in this highly varied subject population.