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

PROTOCOL NO.: A6181061

PROTOCOL TITLE: A Phase 2 Efficacy and Safety Study of SU011248 Administered in a Continuous Daily Regimen in Patients With Cytokine-Refractory Metastatic Renal Cell Carcinoma

Study Centers: Ten centers took part in the study and enrolled subjects; 2 in the United States; 2 in Sweden; 2 in Germany; 1 in France; 1 in Greece; 1 in Netherlands; and 1 in Switzerland.

Study Initiation Date and Final Completion Dates: 25 May 2005 to 15 May 2008

Phase of Development: Phase 2

Study Objectives: Primary Objective: To evaluate the anti-tumor activity of Sunitinib in cytokine-refractory metastatic renal cell cancer (RCC) when administered in a continuous treatment regimen.

Secondary Objectives:

- To evaluate the safety and tolerability of Sunitinib administered in a continuous treatment regimen.
- To evaluate the tolerability of Sunitinib administered in the morning versus in the evening prior to sleep.
- To assess patient reported outcomes (PRO).
- To determine Sunitinib and SU012662 trough concentrations (C_{trough}) for evaluation of steady-state pharmacokinetics.
- To explore the correlations of potential biomarkers with clinical outcomes.

METHODS

Study Design: This study was an open-label, randomized, multicenter, Phase 2 clinical trial of sunitinib using a continuous daily dosing schedule in subjects with metastatic RCC that had failed 1 prior cytokine-based therapy for metastatic disease and had an Eastern

Cooperative Oncology Group (ECOG) performance status of 0 or 1. Open-label trials are customary in the evaluation of agents for the treatment of cancer.

Subjects treated in this study received sunitinib at a starting dose of 37.5 mg/day in repeated 4-week cycles. Cycles could be repeated for up to 1 year in the absence of any withdrawal criteria. The multicenter nature of the study provided reassurance that the results were likely to have general applicability. The schedule of events are summarized in Table 1.

Table 1. Schedule of Events

Procedure		On Treatment[a]					Post-Treatment		
	Screen	Cycle 1		Cycles 2–4		Cycles ≥5	End of Treatment[b]	28 Days Post-Treatment[c]	Survival Follow-Up
	≤21 Days Predose	Day 1	Day 15	Day 1	Day 15	Day 1			
Informed consent	X								
Medical/oncologic history	X								
Physical examination/ECOG/vital signs/weight[d]	X	X[e]		X		X	X	X[f]	
Baseline signs/symptoms		X							
Clinical laboratory tests									
Hematology/chemistry	X	X[e]	X	X	X	X	X	X[f]	
Pregnancy[g]	X								
12-lead electrocardiogram (ECG[h])	X			X[i]			X		
Randomization	X								
Tumor assessments									
Tumor scan/assessment[j]	X			X[k]		X[k]	X		
Other clinical assessments									
Adverse events[l]	X	X	X	X	X	X	X	X	
PRO assessments[m]		X	X	X	X	X	X		
Concomitant medications[n]	X	X	X	X	X	X	X	X	
Study drug dispensation		X		X		X			
Study drug compliance[o]				X		X	X		
Post-study survival status									X[p]
Special laboratory studies									
Trough drug concentration/soluble proteins[q]		X		X		X	X		
Tumor biopsy	X[r]			X[r]		X[r]	X[r]		

Table 1. Schedule of Events

CT = computed tomography; ECOG = eastern cooperative oncology group; MRI = magnetic resonance imaging; PRO = patient-reported outcomes.

a. Cycle 1, Day 1 was the first day study drug was administered; thereafter, assessments had an allowable ±3 day window except for tumor assessments, which were ±7 days. Each cycle was 28 days long. Unless otherwise indicated, all assessments were performed before study drug administration.
b. These assessments did not need to be completed if they were performed within 2 weeks of study withdrawal (within the last 6 weeks for tumor assessments).
c. The 28 day post-treatment visit was not required for subjects continuing treatment on another protocol.
d. Included height at screening only.
e. These assessments were not required if adequate screening assessments had been performed within 7 days.
f. As necessary to follow-up abnormalities or adverse events ongoing at termination.
g. A serum or urine pregnancy test for women of child-bearing potential only.
h. Three 12-lead ECGs performed at least 2 minutes apart.
i. Cycle 2 only.
j. Brain CT or MRI and bone scan required at screening; bone scan after screening required only if bone metastases were present.
k. Even numbered cycles (eg, Cycles 2, 4, 6, etc.) only.
l. Serious adverse events were recorded from the time of signing of the informed consent; all adverse events were recorded from the time of the first dose of study medication until 28 days after the last dose.
m. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) scale and EuroQol 5-dimensional (EQ-5D) questionnaire.
n. Concomitant medications were recorded from 28 days before Cycle 1, Day 1 until 28 days after the last treatment.
o. Bottle(s) and any unused medications were returned for drug accountability.
p. Subjects were contacted (clinic visit or telephone contact) every 2 months after discontinuation for survival status.
q. A 4 mL sample for trough concentrations and a 10 mL sample for soluble protein assessment were collected predosing for subjects in the morning treatment arm only.
r. Optional. Screening could be biopsy or previously collected paraffin block. On-treatment biopsies could be at any time without regard for study day or windows.

Number of Subjects (Planned and Analyzed): A total of 100 subjects were planned in the study; 107 subjects were enrolled and 54 subjects were randomized to receive sunitinib in the morning ("AM" cohort), and 53 subjects were randomized to receive sunitinib in the evening ("PM" cohort) and 24 subjects completed the study.

A total of 107 subjects were enrolled; 40 in France, 17 in Germany, 7 in Greece, 9 in Netherlands, 11 in Sweden, 11 in Switzerland, 12 in the United States.

Diagnosis and Main Criteria for Inclusion: Subjects were required to have histologically proven, unidimensionally measurable, metastatic RCC as per response evaluation criteria in solid tumors (RECIST) that had failed 1 prior cytokine-based therapy for metastatic disease. ECOG performance status of 0 or 1 and adequate vital organ function were also required for eligibility.

The subjects with other than 1 cytokine-based prior therapy or prior sunitinib clinical trial or major surgery, radiation therapy, or systemic therapy within 4 weeks of starting the study treatment were not included in the study. Subjects diagnosed of any second malignancy within the last 3 years, except basal cell carcinoma, squamous cell skin cancer, or in situ carcinoma that has been adequately treated with no evidence of recurrent disease for 12 months were also not included in the study.

Study Treatment: Subjects received 37.5 mg sunitinib malate capsules daily during repeated 4 week cycles. Doses could be increased to 50 mg or reduced to 25 mg based on tolerability. Sunitinib was self-administered orally as a single agent, once daily in the morning or evening (depending on the treatment group) without regard to meals. Sunitinib was provided in 12.5 mg, 25 mg, and 50 mg dose strengths.

Efficacy, Safety, Outcome Research, Pharmacokinetic and Pharmacodynamic Endpoints:

Primary Endpoint: Objective response rate (ORR).

Secondary Endpoints:

- Duration of response (DR).
- Time to tumor progression (TTP).
- Overall survival (OS).
- Progression-free survival (PFS).
- Patient reported outcomes (PROs): Subject-assessed fatigue as measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) Scale and general health status as measured by the EuroQol Group's (EQ-5D) self-report questionnaire (EQ-5D).

- Type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs), laboratory abnormalities.

- C_{trough} concentrations of sunitinib and SU012662, determined from plasma trough samples.

- Plasma concentrations of soluble proteins (such as VEGF, soluble vascular endothelial growth factor receptor 3 [sVEGFR3], sPDGFRβ, and sVEGFR2) that may be associated with tumor proliferation, angiogenesis, or sunitinib mechanism of action.

Safety Evaluations: Safety evaluations included AEs (from the first day of treatment to 28 days after the last dose of study drug); clinical laboratory tests (hematology and serum chemistry); electrocardiogram (ECG); vital signs; and ECOG performance status.

Statistical Methods: The intent-to-treat (ITT) study population was used for all analyses and included all subjects enrolled in the study that received at least 1 dose of study medication.

A sample size of 100 subjects was required to test the null hypothesis that the true response rate was ≤5% versus the alternative hypothesis that the true response rate was ≥15% with 90% power and an alpha level of 0.05. If the number of objective responses was 11 or more, the null hypothesis that the true response rate was ≤5% could be rejected with a target alpha error rate of 0.05.

ORR was summarized as the number and percent of subjects with a confirmed response (Complete response [CR] or Partial response [PR]) with exact 95% confidence intervals (CIs); time-to-event analyses were performed using Kaplan-Meier estimates. PRO endpoints (FACIT-Fatigue and EQ-5D) were scored and assessed as recommended in their respective users' manuals and summarized by using descriptive statistics. Safety analyses were descriptive and included summaries of AEs, serious adverse events SAEs, deaths, discontinuations due to AEs, and clinical laboratory findings, ECG, and vital signs results. AEs were also summarized by Common Terminology Criteria for Adverse Events (CTCAE version 3.0) severity grade, and laboratory results were summarized as shifts from baseline in CTCAE grade.

RESULTS

Subject Disposition and Demography: A total of 107 subjects, 54 on the AM cohort and 53 on the PM cohort, were enrolled and treated. All 107 subjects (100.0%) were treated with sunitinib and qualified for the ITT population. The subject disposition is summarized in Table 2.

Table 2. Subject Disposition

	Sunitinib		Total
	AM Cohort	PM Cohort	
Number of subjects enrolled	54	53	107
Assigned to treatment			
Treated	54 (100)	53 (100)	107 (100)
Completed	15 (27.8)	9 (17.0)	24 (22.4)
Discontinued	39 (72.2)	44 (83.0)	83 (77.6)
Adverse event	7 (13.0)	9 (17.0)	16 (15.0)
Consent withdrawn	1 (1.9)	1 (1.9)	2 (1.9)
Lack of efficacy	31 (57.4)	33 (62.3)	64 (59.8)
Subject died	0 (0.0)	1 (1.9)	1 (0.9)

AM = morning; PM = evening.

The demographic and baseline characteristics are summarized in Table 3.

Table 3. Summary of Demographic and Baseline Characteristics (Intent-to-Treat Population)

Variable	Sunitinib AM (N=54)	Sunitinib PM (N=53)	Total (N=107)
Age (Years)			
n	54	53	107
Mean (SD)	59.3 (9.27)	57.2 (11.48)	58.2 (10.43)
Median	59	59	59
(Min, Max)	(33, 80)	(28, 75)	(28, 80)
Age (Years) (n [%])			
<65 years	37 (68.5)	40 (75.5)	77 (72.0)
≥65 years	17 (31.5)	13 (24.5)	30 (28.0)
Sex (n [%])			
Female	8 (14.8)	11 (20.8)	19 (17.8)
Male	46 (85.2)	42 (79.2)	88 (82.2)
Race (n [%])			
White	30 (55.6)	34 (64.2)	64 (59.8)
Asian	1 (1.9)	2 (3.8)	3 (2.8)
Question not allowed[a]	23 (42.6)	17 (32.1)	40 (37.4)
Weight (kg)			
n	53	53	106
Mean (SD)	80.7 (15.48)	77.4 (15.94)	79.0 (15.73)
Median	79	78	79
(Min, Max)	(50, 136)	(48, 113)	(48, 136)
Height (cm)			
n	54	53	107
Mean (SD)	172.4 (9.73)	172.8 (8.15)	172.6 (8.94)
Median	173	174	173
(Min, Max)	(150, 192)	(154, 196)	(150, 196)
ECOG Performance Status (n [%])			
0	29 (53.7)	32 (60.4)	61 (57.0)
1	25 (46.3)	20 (37.7)	45 (42.1)
>1	0 (0.0)	1 (1.9)	1 (0.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

ECOG = eastern cooperative oncology group; Min = minimum; Max = maximum; n = number of subjects considered for a variable; N = number of subjects in each cohort; SD = standard deviation.

a. All subjects in this category were enrolled in France, where collection of race was not permitted as per the French Regulatory Authority.

Efficacy, Pharmacokinetic, Pharmacodynamic and Outcome Results:

Primary Endpoint: The primary efficacy variable was confirmed OR determined from objective tumor measurements by using RECIST. The ORR is summarized for the ITT population in Table 4. Number of subjects with measurable disease at baseline was 105 and with partial response was 21 subjects. No subjects were with complete response.

Table 4. Summary of Objective Responses Rate

Number of Subjects per Variable	Total (N=107)
Baseline disease assessments	106
Measurable disease at baseline	105
Measurable disease at baseline, correct histological cancer type, and refractory to prior cytokine-based therapy (N+)[a]	105
Best confirmed tumor response (n [%])	
Complete response (CR)	0 (0.0)
Partial response (PR)	21 (20.0)
Stable disease (SD)	53 (50.5)
Progressive disease (PD)	24 (22.9)
Not evaluable (NE)	4 (3.8)
Missing	3 (2.9)
Objective response rate (CR+PR) (n [%])	21 (20.0)
95% exact CI (%)[b]	(12.8 to 28.9)
Duration of stable disease (n)[c]	
>3 months	51
>6 months	36

N = number of subjects; n = number of subjects per variable.
a. This value (N+) was the denominator for percentages in this table.
b. Using exact method based on F distribution.
c. Excludes subjects with a defined confirmed objective response.

Secondary Endpoint: Among the 21 partial responders, 10 subsequently progressed or died while on study (7 in the AM cohort, 3 in the PM cohort). The secondary efficacy endpoints DR, TTP, OS, and PFS are summarized in Table 5.

Table 5. Summary Time-to-Event Analyses (Intent-to-Treat Population)

Variable	Total (N=107)
Duration of response	
Total number of responders (n [%])	21 (20.0)
Number of events on study (n [%])[a, b]	10 (47.6)
Median[c] weeks (95% CI)	32.3 (24.1 to NR)
Time to tumor progression	
Number of events on study (n [%])[d]	66 (62.9)
Median[c] weeks (95% CI)	35.7 (28.0 to 36.3)
Progression-free survival	
Number of events on study (n [%])[d]	68 (64.8)
Median[c] weeks (95% CI)	35.6 (27.9 to 36.3)
Overall survival	
Number of events (n [%])	64 (59.8)
Median[c] weeks (95% CI)	82.9 (69.4 to 106.0)
One-year survival rate (%)	71.7
95% CI	62.1 to 79.3

CI = confidence interval; DR = duration of response; n = number of subjects per variable; N = number of subjects; NR = not reached; OS = overall survival; PFS = progression-free survival; TTP = time to tumor progression.

a. The denominator for DR was the number of responders.
b. On-study included the 28-day follow-up period.
c. Median DR, TTP, OS, and PFS analyses used Kaplan-Meier estimates with 95% CI calculated based on the method of Brookmeyer and Crowley.
d. Percentages for TTP and PFS were based on the number of subjects with measurable disease at baseline, the number of subjects who had the correct histological cancer type, and the number of subjects who had disease that was refractory to prior cytokine-based therapy (105 total).

FACIT Fatigue Scale: Greater than 90% of the expected questionnaires were completed (at least 1 question) at every time point in each cohort through Cycle 10, except Cycle 4, Day 15 in the AM Cohort (87.0%); compliance was more variable in subsequent cycles. The summary of FACIT-fatigue scores and change from Baseline are presented in Table 6.

Table 6. Summary of FACIT-Fatigue Scores and Change From Baseline

	Sunitinib AM Cohort (N=54)				Sunitinib PM Cohort (N=53)			
	Score		Change From Baseline		Score		Change From Baseline	
Time Point	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	52	39.5 (11.41)			52	39.6 (10.15)		
Cycle 1 Day 15	53	37.7 (11.76)	52	-1.9 (9.16)	49	37.0 (11.16)	49	-3.0 (9.42)
Cycle 2 Day 1	51	38.5 (11.95)	50	-0.4 (7.00)	48	37.8 (10.18)	47	-2.7 (8.73)
Cycle 3 Day 1	51	38.4 (10.91)	50	-1.4 (10.53)	47	38.1 (10.64)	46	-2.1 (8.83)
Cycle 4 Day 1	46	39.7 (10.36)	45	-1.7 (10.81)	42	39.2 (10.00)	41	-1.8 (9.23)
Cycle 5 Day 1	39	39.7 (9.80)	38	-1.3 (10.51)	39	37.7 (10.97)	38	-3.4 (8.52)
Cycle 6 Day 1	38	38.9 (10.58)	37	-2.9 (11.69)	35	38.9 (11.23)	34	-3.0 (7.89)
Cycle 7 Day 1	37	38.7 (9.40)	36	-2.9 (11.31)	35	40.2 (8.18)	34	-1.7 (9.23)
Cycle 8 Day 1	34	37.1 (10.72)	33	-3.9 (12.36)	32	40.4 (8.25)	31	-1.8 (7.21)
Cycle 9 Day 1	29	37.8 (10.66)	28	-3.7 (13.18)	28	38.2 (9.93)	27	-3.8 (7.50)
Cycle 10 Day 1	26	38.8 (11.25)	25	-3.8 (10.13)	19	43.5 (7.66)	18	-1.7 (7.76)
Cycle 11 Day 1	24	39.3 (10.35)	23	-3.4 (9.57)	16	44.0 (7.70)	15	-2.2 (8.34)
Cycle 12 Day 1	23	41.0 (10.04)	22	-1.9 (10.32)	18	43.5 (7.39)	17	-1.9 (7.05)
Cycle 13 Day 1	19	40.6 (9.79)	18	-1.4 (10.17)	15	42.4 (7.01)	15	-1.4 (8.45)
End of treatment	16	37.1 (10.50)	16	-7.1 (10.41)	19	33.1 (14.43)	19	-6.6 (12.13)

Possible FACIT-Fatigue scores range from 0 to 52, with 0 being highly fatigued and 52 being not fatigued.
FACIT = functional assessment of chronic illness therapy; N = total number of subjects; SD = standard deviation.

EQ-5D Scores: There was no evidence of a change in the EQ-5D weighted health index from Cycle 1 to Cycle 13 (the last cycle for which results were available for 10 or more subjects in each cohort) on either cohort. For the AM cohort, the median weighted health index was 0.8 at all time points. In the PM cohort, the median was 0.8 at baseline and through Cycle 4, Day 15; thereafter, it was somewhat more variable. However, the range of median scores was set at 0.7 to 1.0.

Sensitivity Analysis of Efficacy: Sensitivity analysis of efficacy results were similar to the primary analysis results reported above which included all subject efficacy data collected on study. All subject efficacy data was collected 1 year after first dose of study treatment ORR, based on the 1 year cutoff, was 20.0% (95% CI: 12.8% to 28.9%), identical to the ORR determined from the full data set. Results for the sensitivity time-to-event analyses are summarized in Table 7.

Table 7. Summary of Time-to-Event Endpoints With 1-Year Cutoff (Both Cohorts Combined)

Variable	Total (N=107)		
	Number (%) Events [a]	Median [b] (Weeks)	95% CI [b]
DR	9 (42.9[c])	32.3	24.1 to NR[d]
TTP	63 (60.0[c])	35.7	28.0 to 36.3
PFS	65 (61.9[c])	35.6	27.9 to 36.3

DR = duration of response; N = total number of subjects; PFS = progression-free survival; TTP = time to tumor progression.

a. For DR, TTP, and PFS, subjects who did not have an event are censored at the time they were last known to have not had the event.
b. Based on Kaplan-Meier estimates.
c. The denominator for DR was the number of responders.
d. NR = not reached.
e. Percentages for TTP and PFS were based on the 105 subjects with measurable disease at baseline, correct histological cancer type, and had disease that was were refractory to prior cytokine-based therapy.

Pharmacokinetic Results: Following continuous daily dosing of sunitinib, the mean trough plasma concentrations (Day 1 of Cycles 2–13) for Sunitinib was 25.45–46.24 ng/mL, its metabolite was 11.08–18.37 ng/mL, and total drug was 37.30–64.60 ng/mL. The summary of sunitinib and its metabolite (SU012662) total drug plasma trough concentrations observed are presented in Table 8. Plasma concentration of total drug (ng/mL) increased moderately from Cycle 2 (sunitinib 41.19 ng/mL, SU012662 15.24 ng/mL, N=22) to Cycle 4 (sunitinib 46.24 ng/mL, SU012662 18.37 ng/mL, N=14); however, this increase was not statistically significant. Plasma levels of both drugs remained relatively stable though the 13 cycles.

Table 8. Mean (± SD) Sunitinib, SU012662, and Total Drug (Sunitinib + SU012662) Trough Plasma Concentrations on Day 1 of Cycles 2-13

Cycle	N	Sunitinib (ng/mL)	SU012662 (ng/mL)	Total Drug (ng/mL)
2	22	41.19±18.82	15.24±8.59	56.43±26.22
3	19	44.24±18.71	17.93±8.61	62.17±26.25
4	14	46.24±13.91	18.37±11.03	64.60±23.51
5	9	38.87±12.70	16.25±9.09	55.11±20.55
6	14	36.96±16.58	15.65±9.68	52.61±24.57
7	10	32.55±11.50	12.31±4.41	44.86±15.19
8	9	29.99±10.41	12.79±5.47	42.78±15.20
9	7	40.34±17.11	15.76±5.29	56.10±22.19
10	9	34.12±15.44	12.85±7.10	46.97±21.44
11	6	42.58±25.09	17.14±10.62	59.72±32.36
12	6	30.48±6.70	11.08±3.97	41.56±8.77
13	2	25.45±1.77	11.85±5.16	37.30±3.39

N = number of subjects with evaluable trough samples; SD = standard deviation.

Dose-corrected (reference dose: 37.5 mg) trough value ranges (Day 1 of Cycles 2–13) for sunitinib, SU012662, and total drug were each generally consistent throughout Cycles 2

through 13. A summary of sunitinib, SU012662, and total drug plasma trough concentrations dose-corrected are presented in Table 9.

Table 9. Mean (± SD) Sunitinib, SU012662, and Total Drug Dose-Corrected Trough Plasma Concentrations on Day 1 of Cycles 2-13

Cycle	N	Sunitinib (ng/mL)	SU012662 (ng/mL)	Total Drug (ng/mL)
2	22	41.56±18.38	15.37±8.46	56.93±25.63
3	19	45.48±17.88	18.46±8.39	63.93±25.16
4	14	46.57±17.37	18.69±12.22	65.26±28.36
5	9	39.63±13.40	15.81±6.60	55.44±18.41
6	14	35.09±14.46	14.58±7.88	49.67±21.02
7	10	33.52±13.60	12.83±5.50	46.35±18.64
8	9	30.71±7.52	12.95±4.17	43.66±10.49
9	7	44.30±32.36	16.78±10.19	61.08±42.46
10	9	39.46±17.73	14.17±5.04	53.62±21.35
11	6	48.17±42.63	17.44±10.50	65.60±51.43
12	6	34.08±12.52	11.94±4.00	46.02±14.90
13	2	32.13±11.21	13.90±2.26	46.03±8.94

N = number of subjects with evaluable trough samples; SD = standard deviation.

Pharmacodynamic Results:

Plasma Levels of VEGF, sVEGFR-2, and sVEGFR-3 during Sunitinib Treatment in Subjects with Metastatic RCC: In response to dosing in Cycle 1, mean VEGF levels increased by 2.43-fold, and mean sVEGFR-2 and sVEGFR-3 levels decreased by 0.63- and 0.57-fold, respectively, compared to baseline, and remained at steady-state levels throughout the study.

Plasma Trough Drug Concentrations Versus Changes in Plasma Biomarker Protein Levels: Linear regression analysis revealed a statistically significant correlation between drug levels (nominal C_{trough} of sunitinib alone) and change in mean plasma protein levels on Day 1 of Cycle 2 for each soluble protein (VEGF: R^2 =0.348; p value = 0.004; sVEGFR-2 R^2 = 0.449; p value = 0.001; sVEGFR-3: R^2 =0.481; p value = 0.002).

For sVEGFR-2, the correlation was also statistically significant on Day 1 of each cycle through Cycle 7 (R^2 range: 0.330 – 0.797; p value range: 0.000 – 0.042), although only 8 subjects' samples were analyzed for Day 1 of Cycles 5 and 7 and 2 subjects' samples for Day 1 of Cycle 10.

For sVEGFR-3, the correlation was statistically significant on Day 1 of Cycles 5 (p value, R2 value) and 6 (p value, R^2 value).

Association of Plasma Biomarker Level Changes with Measures of Clinical Benefit: Potential associations between levels of soluble proteins and measures of clinical benefit (time-to-event analyses) were assessed. Levels of soluble protein at Baseline and the changes from baseline (ratio of values to baseline) were compared by time point between subjects stratified by tumor response. Changes in the levels of soluble proteins were compared between the subjects with a PR, CR, or Stable Disease for greater than 6 weeks (as

assessed by RECIST) and subjects with a recorded best response of disease progression (progressive disease; [PD]) in Table 10.

Table 10. Comparison of Levels of Soluble Protein Biomarkers at Baseline[a] and Changes From Baseline (Intent-to-Treat Population: Sunitinib AM)

Variable	Sunitinib (N=54)							
							p-Value	
	CR or PR or (SD ≥6 Weeks)			PD			Wilcoxon RS Test (2-Sided)	t-Test (2-Sided)
	Mean	Median	n	Mean	Median	n		
VEGF (pg/mL) Baseline	169.94	92.7	38	119.12	94.5	11	0.914	0.466
C2D1:C1D1	2.36	1.78	36	2.66	2.17	11	0.28	0.748
C3D1:C1D1	2.15	1.85	34	3.17	2.16	8	0.236	0.158
C4D1:C1D1	1.98	1.83	33	1.58	1.7	8	0.587	0.342
C5D1:C1D1	1.81	1.49	31	1.9	1.52	7	0.706	0.869
C6D1:C1D1	2.16	1.95	33	1.67	1.7	5	0.353	0.342
C7D1:C1D1	2.08	1.86	26	1.83	1.63	4	0.807	0.732
C10D1:C1D1	2.3	2.17	7	2.62	1.83	3	1	0.656
VEGFR2 (pg/mL) Baseline	10515.95	10378	38	10168.18	10388	11	0.857	0.66
C2D1:C1D1	0.65	0.67	36	0.61	0.59	11	0.308	0.509
C3D1:C1D1	0.56	0.56	34	0.61	0.57	8	0.987	0.401
C4D1:C1D1	0.53	0.52	33	0.59	0.59	8	0.236	0.244
C5D1:C1D1	0.51	0.5	31	0.56	0.54	7	0.274	0.341
C6D1:C1D1	0.51	0.48	33	0.49	0.51	5	1	0.812
C7D1:C1D1	0.52	0.51	26	0.52	0.53	4	0.855	0.943
C10D1:C1D1	0.45	0.45	7	0.41	0.41	3	0.36	0.576
VEGFR3 (pg/mL) Baseline	54163.16	49200	38	53440	56850	10	0.316	0.923
C2D1:C1D1	0.61	0.6	24	0.48	0.44	7	0.026	0.027
C3D1:C1D1	0.57	0.55	18	0.67	0.59	3	0.268	0.278
C4D1:C1D1	0.58	0.59	19	0.71	0.7	4	0.417	0.188
C5D1:C1D1	0.57	0.53	16	0.63	0.66	4	0.449	0.47
C6D1:C1D1	0.58	0.54	16	0.61	0.67	3	0.867	0.834
C7D1:C1D1	0.65	0.56	13	0.83	0.83	2	0.106	0.528
C10D1:C1D1	0.68	0.58	3	0.7	0.7	2	0.773	0.921

CNDN: C1D1 refers to ratios to baseline at specific cycle and day during treatment.
CR = complete response, N = number of subjects; n = number of subjects per variable; PR = partial response, SD = stable disease, PD = progressive disease; VEGFR = vascular endothelial growth factor receptor.
a. Cycle 1 Day 1 result.

Safety Results: The analysis population used for safety analyses included all subjects who received at least 1 dose of sunitinib (ITT population). All 107 subjects (100.0%) experienced AEs, and 106 subjects (99.1%) experienced AEs that were considered related to the study drug. Forty-one subjects (38.3%) experienced serious AEs, and 24 subjects (22.4%) experienced SAEs considered related to the study drug.

AEs were generally similar on the 2 cohorts, with the exception of nausea (46.3% versus 35.8% for the AM and PM cohorts, respectively), dyspepsia (40.7% versus 28.3%), epistaxis (31.5% versus 20.8%), mucosal inflammation (29.6% versus 17.0%), constipation (25.9% versus 15.1%), and abdominal pain upper (24.1% versus 11.3%).

The most frequently experienced adverse events (those experienced by ≥5% subjects) are summarized by preferred term in decreasing order of frequency in Table 11.

Table 11. Treatment-Emergent Adverse Events at ≥5% Threshold (Intent-to-Treat Population)

Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any adverse event	54 (100.0)	1341	53 (100.0)	1322	107 (100.0)	2663
Diarrhoea	41 (75.9)	142	40 (75.5)	137	81 (75.7)	279
Palmar-plantar erythrodysaesthesia syndrome	28 (51.9)	58	23 (43.4)	62	51 (47.7)	120
Hypertension	25 (46.3)	39	23 (43.4)	47	48 (44.9)	86
Stomatitis	25 (46.3)	50	21 (39.6)	57	46 (43.0)	107
Asthenia	24 (44.4)	88	20 (37.7)	83	44 (41.1)	171
Nausea	25 (46.3)	34	19 (35.8)	33	44 (41.1)	67
Anorexia	21 (38.9)	31	20 (37.7)	34	41 (38.3)	65
Fatigue	19 (35.2)	27	22 (41.5)	31	41 (38.3)	58
Hair colour changes	18 (33.3)	18	20 (37.7)	20	38 (35.5)	38
Dyspepsia	22 (40.7)	30	15 (28.3)	19	37 (34.6)	49
Vomiting	16 (29.6)	27	18 (34.0)	31	34 (31.8)	58
Weight decreased	15 (27.8)	32	17 (32.1)	41	32 (29.9)	73
Dysgeusia	13 (24.1)	17	15 (28.3)	16	28 (26.2)	33
Epistaxis	17 (31.5)	23	11 (20.8)	12	28 (26.2)	35
Abdominal pain	14 (25.9)	16	13 (24.5)	16	27 (25.2)	32
Mucosal inflammation	16 (29.6)	25	9 (17.0)	10	25 (23.4)	35
Rash	12 (22.2)	17	11 (20.8)	15	23 (21.5)	32
Constipation	14 (25.9)	15	8 (15.1)	11	22 (20.6)	26
Dry skin	10 (18.5)	11	12 (22.6)	15	22 (20.6)	26
Pain in extremity	11 (20.4)	15	11 (20.8)	16	22 (20.6)	31
Abdominal pain upper	13 (24.1)	14	6 (11.3)	7	19 (17.8)	21
Erythema	11 (20.4)	13	8 (15.1)	8	19 (17.8)	21
Pyrexia	9 (16.7)	11	10 (18.9)	12	19 (17.8)	23
Chest pain	9 (16.7)	13	9 (17.0)	15	18 (16.8)	28
Arthralgia	9 (16.7)	11	8 (15.1)	14	17 (15.9)	25
Anaemia	7 (13.0)	9	9 (17.0)	13	16 (15.0)	22
Cough	6 (11.1)	11	10 (18.9)	12	16 (15.0)	23
Back pain	8 (14.8)	13	6 (11.3)	13	14 (13.1)	26

Table 11. Treatment-Emergent Adverse Events at ≥5% Threshold (Intent-to-Treat Population)

Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Haemoptysis	8 (14.8)	10	6 (11.3)	6	14 (13.1)	16
Headache	6 (11.1)	8	8 (15.1)	8	14 (13.1)	16
Oedema peripheral	9 (16.7)	10	5 (9.4)	5	14 (13.1)	15
Thrombocytopenia	8 (14.8)	21	6 (11.3)	11	14 (13.1)	32
Dizziness	9 (16.7)	11	4 (7.5)	6	13 (12.1)	17
Dyspnoea	6 (11.1)	11	7 (13.2)	9	13 (12.1)	20
Insomnia	4 (7.4)	4	8 (15.1)	8	12 (11.2)	12
Neutropenia	5 (9.3)	8	7 (13.2)	18	12 (11.2)	26
Ageusia	4 (7.4)	4	7 (13.2)	9	11 (10.3)	13
Skin discolouration	4 (7.4)	5	7 (13.2)	7	11 (10.3)	12
Myalgia	2 (3.7)	2	8 (15.1)	8	10 (9.3)	10
Nasopharyngitis	6 (11.1)	7	4 (7.5)	4	10 (9.3)	11
Oral pain	4 (7.4)	4	6 (11.3)	7	10 (9.3)	11
Alopecia	6 (11.1)	6	3 (5.7)	5	9 (8.4)	11
Dehydration	1 (1.9)	1	8 (15.1)	15	9 (8.4)	16
Flatulence	1 (1.9)	1	8 (15.1)	9	9 (8.4)	10
Blood lactate dehydrogenase increased	6 (11.1)	6	2 (3.8)	2	8 (7.5)	8
Glossodynia	5 (9.3)	6	3 (5.7)	3	8 (7.5)	9
Haemorrhage	4 (7.4)	4	4 (7.5)	4	8 (7.5)	8
Vitamin B12 deficiency	6 (11.1)	6	2 (3.8)	2	8 (7.5)	8
Blood creatinine increased	1 (1.9)	1	6 (11.3)	7	7 (6.5)	8
Chills	4 (7.4)	4	3 (5.7)	4	7 (6.5)	8
Gastrooesophageal reflux disease	0 (0.0)	0	7 (13.2)	11	7 (6.5)	11
Haemorrhoids	4 (7.4)	4	3 (5.7)	3	7 (6.5)	7
Rectal haemorrhage	5 (9.3)	7	2 (3.8)	2	7 (6.5)	9
Vertigo	4 (7.4)	6	3 (5.7)	3	7 (6.5)	9
Blood alkaline phosphatase increased	2 (3.7)	3	4 (7.5)	6	6 (5.6)	9
Bronchitis	4 (7.4)	5	2 (3.8)	2	6 (5.6)	7
Dysphagia	2 (3.7)	2	4 (7.5)	4	6 (5.6)	6
Gingival bleeding	3 (5.6)	4	3 (5.7)	5	6 (5.6)	9
Hyperkalaemia	3 (5.6)	3	3 (5.7)	5	6 (5.6)	8
Hyperkeratosis	2 (3.7)	2	4 (7.5)	4	6 (5.6)	6
Leukopenia	3 (5.6)	8	3 (5.7)	6	6 (5.6)	14
Oral herpes	3 (5.6)	3	3 (5.7)	4	6 (5.6)	7
Pruritus	1 (1.9)	1	5 (9.4)	5	6 (5.6)	6
Urinary tract infection	5 (9.3)	7	1 (1.9)	1	6 (5.6)	8

The adverse events and serious adverse events were not separated out.
% = (n/N)*100.
N = number of subjects; n = number of subjects per cohort.

The summary of treatment-related AEs experienced by ≥5% of subjects (ITT population) are presented in Table 12.

Table 12. Summary of Treatment-Related Adverse Events Experienced by ≥5% of Subjects (Intent-to-Treat Population)

Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any adverse event	54 (100.0)	995	52 (98.1)	1004	106 (99.1)	1999
Diarrhoea	40 (74.1)	138	40 (75.5)	136	80 (74.8)	274
Palmar-plantar erythro-dysaesthesia syndrome	28 (51.9)	58	23 (43.4)	62	51 (47.7)	120
Hypertension	24 (44.4)	37	23 (43.4)	46	47 (43.9)	83
Stomatitis	25 (46.3)	50	21 (39.6)	57	46 (43.0)	107
Asthenia	24 (44.4)	84	20 (37.7)	82	44 (41.1)	166
Anorexia	21 (38.9)	31	19 (35.8)	29	40 (37.4)	60
Nausea	23 (42.6)	31	17 (32.1)	29	40 (37.4)	60
Fatigue	19 (35.2)	25	20 (37.7)	29	39 (36.4)	54
Hair colour changes	18 (33.3)	18	20 (37.7)	20	38 (35.5)	38
Dyspepsia	20 (37.0)	28	14 (26.4)	18	34 (31.8)	46
Vomiting	14 (25.9)	24	15 (28.3)	22	29 (27.1)	46
Dysgeusia	13 (24.1)	17	15 (28.3)	16	28 (26.2)	33
Epistaxis	17 (31.5)	23	11 (20.8)	12	28 (26.2)	35
Weight decreased	12 (22.2)	28	16 (30.2)	40	28 (26.2)	68
Mucosal inflammation	16 (29.6)	25	9 (17.0)	10	25 (23.4)	35
Rash	11 (20.4)	15	11 (20.8)	14	22 (20.6)	29
Dry skin	8 (14.8)	9	11 (20.8)	14	19 (17.8)	23
Erythema	11 (20.4)	13	7 (13.2)	7	18 (16.8)	20
Thrombocytopenia	8 (14.8)	21	6 (11.3)	10	14 (13.1)	31
Abdominal pain	7 (13.0)	8	6 (11.3)	6	13 (12.1)	14
Abdominal pain upper	8 (14.8)	9	4 (7.5)	4	12 (11.2)	13
Neutropenia	5 (9.3)	8	7 13.2)	18	12 (11.2)	26
Pain in extremity	6 (11.1)	7	6 (11.3)	8	12 (11.2)	15
Ageusia	4 (7.4)	4	7 (13.2)	9	11 (10.3)	13
Anaemia	5 (9.3)	7	5 (9.4)	7	10 (9.3)	14
Oral pain	4 (7.4)	4	6 (11.3)	7	10 (9.3)	11
Skin discolouration	3 (5.6)	4	7 (13.2)	7	10 (9.3)	11
Alopecia	6 (11.1)	6	3 (5.7)	5	9 (8.4)	11
Dizziness	5 (9.3)	5	4 (7.5)	6	9 (8.4)	11
Flatulence	1 (1.9)	1	8 (15.1)	8	9 (8.4)	9
Arthralgia	2 (3.7)	2	6 (11.3)	10	8 (7.5)	12
Constipation	5 (9.3)	5	3 (5.7)	4	8 (7.5)	9
Dehydration	1 (1.9)	1	7 (13.2)	12	8 (7.5)	13
Glossodynia	5 (9.3)	6	3 (5.7)	3	8 (7.5)	9
Myalgia	1 (1.9)	1	7 (13.2)	7	8 (7.5)	8
Vitamin B12 deficiency	6 (11.1)	6	2 (3.8)	2	8 (7.5)	8
Haemorrhage	3 (5.6)	3	4 (7.5)	4	7 (6.5)	7
Cough	2 (3.7)	2	4 (7.5)	4	6 (5.6)	6
Gastrooesophageal reflux disease	0 (0.0)	0	6 (11.3)	10	6 (5.6)	10
Gingival bleeding	3 (5.6)	4	3 (5.7)	5	6 (5.6)	9
Headache	1 (1.9)	1	5 (9.4)	5	6 (5.6)	6
Hyperkeratosis	2 (3.7)	2	4 (7.5)	4	6 (5.6)	6
Leukopenia	3 (5.6)	8	3 (5.7)	6	6 (5.6)	14
Oedema peripheral	3 (5.6)	3	3 (5.7)	3	6 (5.6)	6

Table 12. Summary of Treatment-Related Adverse Events Experienced by ≥5% of Subjects (Intent-to-Treat Population)

Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Pruritus	1 (1.9)	1	5 (9.4)	5	6 (5.6)	6
Vertigo	3 (5.6)	4	3 (5.7)	3	6 (5.6)	7

The adverse events and serious adverse events were not separated out.
% = (n/N)*100.
N = number of subjects; n = number of subjects per cohort.

Forty-one subjects experienced a total of 135 SAEs. There was no evidence of a difference in the type of frequency of SAEs between the 2 cohorts A summary of All-Causality SAEs at no higher than a 5% threshold are presented in Table 13.

Table 13. Summary of All Serious Adverse Events (Intent-to-Treat Population)

Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any adverse event	21 (38.9)	73	20 (37.7)	62	41 (38.3)	135
Abdominal pain	4 (7.4)	4	3 (5.7)	3	7 (6.5)	7
Anorexia	1 (1.9)	1	3 (5.7)	3	4 (3.7)	4
Dehydration	1 (1.9)	1	3 (5.7)	3	4 (3.7)	4
Thrombocytopenia	3 (5.6)	3	1 (1.9)	1	4 (3.7)	4
Anemia	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Asthenia	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Disease progression	0 (0.0)	0	3 (5.7)	3	3 (2.8)	3
Dizziness	2 (3.7)	3	1 (1.9)	1	3 (2.8)	4
Dyspnea	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Hematemesis	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Vomiting	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Anuria	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Confusional state	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Epistaxis	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Fatigue	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Gait disturbance	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Hemoptysis	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Hyperkalemia	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Hypoglycemia	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Mucosal inflammation	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Nausea	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Edema peripheral	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Esophagitis	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Perirectal abscess	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Pyrexia	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Subileus	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Syncope	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Urinary retention	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Acute myeloid leukemia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Aspiration pleural cavity	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Benign prostatic hyperplasia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Blood creatinine increased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Bone lesion	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Brain edema	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Burn Oesophageal	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Cardiac arrest	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Cardiac failure congestive	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Cerebrovascular accident	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Cholangitis acute	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Constipation	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Depressed level of conscious	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Dermatitis allergic	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Diabetes mellitus	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Diarrhea	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Dysesthesia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Eye pain	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Fall	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Flank pain	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Gastritis hemorrhagic	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Gastrointestinal hemorrhage	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Hematuria	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hypercalcemia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hyperglycemia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1

Table 13. Summary of All Serious Adverse Events (Intent-to-Treat Population)

Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Hypernatremia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hyponatremia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hypothermia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Malignant ascites	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Malignant neoplasm progression	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Malnutrition	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Melena	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Multi-organ failure	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Muscular weakness	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Nocturnal dyspnea	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Obstructive uropathy	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Organ failure	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Osteonecrosis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Pain in extremity	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Palmar-plantar erythrodysesthesia syndrome	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Pancreatitis acute	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Paresis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Pelvic pain	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Performance status decreased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Peripheral sensory neuropathy	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Pleural effusion	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Pleurodesis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Pneumonia	1 (1.9)	2	0 (0.0)	0	1 (0.9)	2
Renal failure	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Renal failure acute	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Renal hemorrhage	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Respiratory tract infection	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Salivary hypersecretion	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Sepsis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Stomatitis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Tumor pain	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Urinary tract infection	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Vertigo	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Wound	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1

N = number of subjects.

Treatment-related SAEs that were experienced by more than 1 subject were dehydration and thrombocytopenia, anorexia, asthenia, dizziness, and hematemesis, and anemia, epistaxis, esophagitis, fatigue, mucosal inflammation, and vomiting. A summary of treatment-related SAEs (ITT population) are presented in Table 14.

Table 14. Summary of Treatment-Related Serious Adverse Events (Intent-to-Treat Population)

Preferred Term	Sunitinib AM Cohort		Sunitinib PM Cohort		Total	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any adverse event	12 (22.2)	28	12 (22.6)	27	24 (22.4)	55
Dehydration	1 (1.9)	1	3 (5.7)	3	4 (3.7)	4
Thrombocytopenia	3 (5.6)	3	1 (1.9)	1	4 (3.7)	4
Anorexia	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Asthenia	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Dizziness	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Hematemesis	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Anemia	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Epistaxis	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Esophagitis	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Fatigue	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Mucosal inflammation	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Vomiting	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Abdominal pain	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Acute myeloid leukemia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Blood creatinine increased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Brain edema	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Burn esophageal	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Cardiac failure congestive	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Diarrhea	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Gait disturbance	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Gastritis hemorrhagic	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Gastrointestinal hemorrhage	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Hypernatremia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hyponatremia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Malnutrition	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Melena	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Muscular weakness	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Nausea	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Palmar-plantar erythrodysesthesia syndrome	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Pelvic pain	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Perirectal abscess	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Pyrexia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Renal failure	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Stomatitis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Vertigo	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1

ITT = intend to treat; n = number of subjects.

Permanent Discontinuations Due to Adverse Events: AEs that led to discontinuation are summarized in Table 15.

Table 15. Summary of Adverse Events That led to Treatment Discontinuation

SOC Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	n (SD)	Number of Events	n (SD)	Number of Events	n (SD)	Number of Events
Any adverse event	9 (16.7)	14	10 (18.9)	16	19 (17.8)	30
Blood and lymphatic system disorders	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Thrombocytopenia	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Cardiac disorders	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Cardiac failure congestive	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Gastrointestinal disorders	3 (5.6)	4	3 (5.7)	4	6 (5.6)	8
Diarrhoea	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Stomatitis	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Abdominal pain	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Gastritis haemorrhagic	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Haematemesis	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Vomiting	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
General disorders and administration site conditions	4 (7.4)	4	7 (13.2)	7	11 (10.3)	11
Asthenia	3 (5.6)	3	1 (1.9)	1	4 (3.7)	4
Disease progression	0 (0.0)	0	4 (7.5)	4	4 (3.7)	4
Fatigue	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Oedema peripheral	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Pyrexia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Injury, poisoning and procedural complications	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Accidental overdose	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Investigations	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Blood creatinine increased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Metabolism and nutrition disorders	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Anorexia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hypernatraemia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Malignant ascites	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Nervous system disorders	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Quadriplegia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Respiratory, thoracic and mediastinal disorders	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Haemoptysis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1

N = number of subjects; n = number of subjects with adverse event; SD = standard deviation; SOC = system organ class.

Dose Reductions or Delays due to Adverse Events: Subjects who had a dose reduction or delay because of AEs are summarized in Table 16. Overall, 69 subjects experienced a dose reduction or delay because of adverse events at some time during the study. Adverse events that most commonly led to dose reductions or delays included gastrointestinal disorders (32 subjects, 29.9%; including diarrhea [14 subjects] and vomiting [11 subjects]), general disorders and administration site conditions (27 subjects, 25.2%; including asthenia [17 subjects]), skin and subcutaneous tissue disorders (19 subjects, 17.8%; including palmar-plantar erythrodysesthesia syndrome [15 subjects]), and metabolism and nutrition disorders (13 subjects, 12.1%).

Table 16. Summary of Adverse Events That led to a Delay or Change in Study Drug Dose

SOC Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	n (SD)	Number of Events	n (SD)	Number of Events	n (SD)	Number of Events
Any adverse event	35 (64.8)	114	34 (64.2)	114	69 (64.5)	228
Blood and lymphatic system disorders	6 (11.1)	9	8 (15.1)	11	14 (13.1)	20
Thrombocytopenia	3 (5.6)	5	4 (7.5)	4	7 (6.5)	9
Neutropenia	1 (1.9)	1	4 (7.5)	6	5 (4.7)	7
Anaemia	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Leukopenia	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Ear and labyrinth disorders	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Vertigo	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Eye disorders	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Vision blurred	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Gastrointestinal disorders	15 (27.8)	35	17 (32.1)	34	32 (29.9)	69
Diarrhoea	4 (7.4)	9	10 (18.9)	12	14 (13.1)	21
Vomiting	6 (11.1)	7	5 (9.4)	5	11 (10.3)	12
Nausea	3 (5.6)	3	4 (7.5)	4	7 (6.5)	7
Stomatitis	1 (1.9)	1	5 (9.4)	7	6 (5.6)	8
Abdominal pain	2 (3.7)	2	2 (3.8)	3	4 (3.7)	5
Gingivitis	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Abdominal pain upper	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Aphthous stomatitis	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Atrophy of tongue papillae	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Duodenal ulcer haemorrhage	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Gastric ulcer	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Gastrointestinal haemorrhage	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Glossitis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Haematemesis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Haematochezia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Hiatus hernia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Melaena	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Oesophagitis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Oesophagitis ulcerative	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Oral pain	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
General disorders and administration site conditions	13 (24.1)	15	14 (26.4)	20	27 (25.2)	35
Asthenia	7 (13.0)	7	10 (18.9)	13	17 (15.9)	20
Fatigue	2 (3.7)	2	4 (7.5)	4	6 (5.6)	6
Mucosal inflammation	2 (3.7)	4	1 (1.9)	1	3 (2.8)	5
Gait disturbance	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Malaise	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Performance status decreased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Pyrexia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hepatobiliary disorders	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Cholangitis acute	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Infections and infestations	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Urinary tract infection	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Injury, poisoning and procedural complications	3 (5.6)	4	1 (1.9)	1	4 (3.7)	5
Burn oesophageal	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2

Table 16. Summary of Adverse Events That led to a Delay or Change in Study Drug Dose

SOC Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	n (SD)	Number of Events	n (SD)	Number of Events	n (SD)	Number of Events
Fall	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Upper limb fracture	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Wound	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Investigations	2 (3.7)	2	5 (9.4)	8	7 (6.5)	10
Blood alkaline phosphatase increased	0 (0.0)	0	2 (3.8)	2	2 (1.9)	2
Alanine aminotransferase increased	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Blood amylase increased	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Blood creatinine increased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Platelet count	0 (0.0)	0	1 (1.9)	4	1 (0.9)	4
Weight decreased	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Metabolism and nutrition disorders	7 (13.0)	9	6 (11.3)	10	13 (12.1)	19
Anorexia	4 (7.4)	5	4 (7.5)	5	8 (7.5)	10
Hyperkalaemia	2 (3.7)	2	1 (1.9)	1	3 (2.8)	3
Dehydration	0 (0.0)	0	2 (3.8)	3	2 (1.9)	3
Hyperglycaemia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Hyponatraemia	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Malnutrition	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Musculoskeletal and connective tissue disorders	4 (7.4)	5	2 (3.8)	2	6 (5.6)	7
Pain in extremity	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Bone lesion	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Bone pain	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Flank pain	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Muscular weakness	1 (1.9)	2	0 (0.0)	0	1 (0.9)	2
Nervous system disorders	5 (9.3)	7	1 (1.9)	1	6 (5.6)	8
Dizziness	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Syncope	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Dysaesthesia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Headache	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Paresis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Spinal cord compression	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Psychiatric disorders	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Confusional state	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Depression	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Renal and urinary disorders	3 (5.6)	6	1 (1.9)	3	4 (3.7)	9
Anuria	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Haematuria	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Urinary retention	1 (1.9)	1	1 (1.9)	1	2 (1.9)	2
Obstructive uropathy	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Renal haemorrhage	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Urinary hesitation	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Reproductive system and breast disorders	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Benign prostatic hyperplasia	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Respiratory, thoracic and mediastinal disorders	3 (5.6)	3	3 (5.7)	4	6 (5.6)	7

Table 16. Summary of Adverse Events That led to a Delay or Change in Study Drug Dose

SOC Preferred Term	Sunitinib AM (N=54)		Sunitinib PM (N=53)		Total Drug (N=107)	
	n (SD)	Number of Events	n (SD)	Number of Events	n (SD)	Number of Events
Epistaxis	3 (5.6)	3	1 (1.9)	1	4 (3.7)	4
Cough	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Dyspnoea	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Pleural effusion	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Skin and subcutaneous tissue disorders	7 (13.0)	9	12 (22.6)	16	19 (17.8)	25
Palmar—plantar erythrodysaes—thesia syndrome	4 (7.4)	5	11 (20.8)	13	15 (14.0)	18
Hyperkeratosis	2 (3.7)	2	0 (0.0)	0	2 (1.9)	2
Dermatitis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Dermatitis allergic	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Hyperhidrosis	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Rash	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Skin discolouration	0 (0.0)	0	1 (1.9)	1	1 (0.9)	1
Vascular disorders	3 (5.6)	3	2 (3.8)	2	5 (4.7)	5
Hypertension	1 (1.9)	1	2 (3.8)	2	3 (2.8)	3
Haemorrhage	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1
Hot flush	1 (1.9)	1	0 (0.0)	0	1 (0.9)	1

% = (n/N)*100.
N = number of subjects; n = number of subjects with adverse event; SD = standard deviation; SOC = system organ class.

Deaths: Six subjects (5.6%; 1 in the AM cohort and 5 in the PM cohorts) died on study treatment (ie, after their first dose and within 28 days of their last dose of study medication), and 58 subjects (54.2%; 29 versus 29 subjects) died during follow-up (>28 days after the last dose of study medication). The summary of deaths are presented in Table 17.

Table 17. Summary of Deaths

Variable	Sunitinib AM (N=54)	Sunitinib PM (N=53)	Total Drug (N=107)
Subjects who died	30 (55.6)	34 (64.2)	64 (59.8)
Subjects who died on-study [a]	1 (1.9)	5 (9.4)	6 (5.6)
Disease under study	1 (1.9)	5 (9.4)	6 (5.6)
Subjects who died in follow-up [b]	29 (53.7)	29 (54.7)	58 (54.2)
automobile accident	0 (0.0)	1 (1.9)	1 (0.9)
Disease under study	27 (50.0)	27 (50.9)	54 (50.5)
Unknown	1 (1.9)	1 (1.9)	2 (1.9)
Study treatment, death due to acute myoblastic leukemia	1 (1.9)	0 (0.0)	1 (0.9)

N = number of subjects.
a. On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug.
b. Follow-up deaths are those that occurred more than 28 days after the last dose of study drug.

Clinical Laboratory Test Results: There was considerable variability between subjects for most hematology tests. In general, there appeared to be a mean decrease from Baseline to

Cycle 2, Day 1 in levels of platelets, white blood cell (WBC), monocytes, absolute neutrophil count (ANC), and segmented neutrophils. For these measures, there did not appear to be a continued mean change during additional cycles beyond Cycle 2, Day 1. For all hematology tests, results were similar between the 2 cohorts.

There was considerable variability between subjects for most serum chemistry tests, but there was no evidence of a clinically significant change in the mean with time after dosing for any test. For all serum chemistry tests, results were similar between the 2 cohorts.

Vital Signs: Forty-eight subjects (25 and 23 in the AM and PM Cohorts, respectively) experienced AEs of hypertension, including a total of 12 (11.2%) subjects: 6 subjects in the AM cohort and 6 subjects in the PM cohort experienced a total of 22 Grade 3 hypertension events; no subjects experienced hypertension above Grade 3. All reported cases of Grade 3 hypertension included at least 1 event that was treatment-related.

Electrocardiogram: ECG was performed at Baseline, Cycle 2, Day 1, at the end of study, and otherwise as clinically indicated. The mean change from baseline to Cycle 2 Day 1 in QTc interval was 2.0 msec (standard deviation: 24.97 msec). No subjects experienced a Grade 3 or 4 QTc interval prolongation.

CONCLUSIONS: Sunitinib 37.5 mg on a continuous daily dosing (CDD) schedule demonstrated clinically relevant antitumor activity with an overall ORR of 20.0% and a median PFS of 8.2 months in subjects with cytokine-refractory metastatic RCC.

The AE profile of sunitinib 37.5 mg on a CDD schedule was generally tolerable and manageable in this subject population and appeared similar between AM and PM cohorts.

Health-related quality of life based on available FACIT-Fatigue and EQ-5D questionnaire results was maintained by sunitinib malate treatment in this study.

Following CDD with sunitinib, the steady-state sunitinib and SU012662 concentrations were reached within the first cycle without disproportionate accumulation of sunitinib and SU012662 throughout the study.

Changes in circulating VEGF, sVEGFR-2, and sVEGFR-3 biomarker levels were not found to be associated with measures of clinical benefit in this study.