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

PROTOCOL NO.: A6181078

PROTOCOL TITLE: A Treatment Protocol for Patients Continuing From a Prior SU-011248 Protocol

Study Centers: Sixty centers took part in the study and enrolled subjects; 36 in the United States (US), 6 each in Canada and Italy, 4 in Germany, 3 each in France and Spain, and 2 in the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 23 May 2006 to 16 December 2011. This study was terminated prematurely by the Sponsor.

Phase of Development: Not Applicable

Study Objectives:

Primary Objective: To provide access to sunitinib treatment for subjects who had participated in previous sunitinib protocols and had the potential to derive clinical benefit from sunitinib treatment as judged by the Investigator.

Secondary Objectives:

- To assess the safety of sunitinib administered in the regimens included in this study.
- To continue follow-up of efficacy endpoints of interest in previous sunitinib studies contributing to this protocol.

METHODS:

Study Design: This was an open-label study. During this study, subjects continued to receive sunitinib in the regimen used in their previous study (including the combination regimen previously received by that subject) or adopted 1 of the standard sunitinib schedules (ie, Schedule 4/2 [4 weeks on study drug, 2 weeks off treatment], Schedule 2/1 [2 weeks on study drug, 1 week off treatment], Schedule 2/2 [2 weeks on study drug, 2 weeks off treatment], or continuous dosing). Dose reductions were allowed based on tolerability. Subjects who did not receive sunitinib in their prior study (eg, assigned to placebo in their previous study) were treated with sunitinib at a dose and schedule for which there was sufficient safety data. Disease assessments for tumor response and progression were performed for data collection on selected subjects; specifically, subjects who previously participated in a study for which objective disease response or time-to-progression was a

study endpoint. For individual subjects enrolling from protocols that included a survival endpoint, follow-up survival information was collected approximately every 2 months until death or up to 2 years from the date of the last dose of sunitinib. Subjects continued to be treated with sunitinib on this protocol as long as there was evidence of clinical benefit in the judgment of the Investigator.

The schedule of activities during the study is provided in Table 1.

Table 1. Schedule of Activities

Protocol Activities[a]	Screen	Start of Treatment (Cycle 1)	First Exposure or Changing Dosing Regimen[b]	All Other Cycles[c]	End of Treatment/ Withdrawal	Post-Treatment Follow-up[d]	Survival Follow-Up
	Days -42 to 1	**Day 1**	**Refer to Table 2**	**Day 1**			
Informed consent	X						
Physical examination	(X)[e]	(X)[f]	X	X	X	(X)[g]	
Laboratory studies							
Hematology[h]	(X)[e]	(X)[f]	X	X	X	(X)[g]	
Biochemistry[h]	(X)[e]	(X)[f]	X	X	X	(X)[g]	
Urinalysis[i]	(X)[e]			(X)	X		
Coagulation[j]	(X)				(X)		
Thyroid function testing		only performed if clinically indicated			(X)		
Pregnancy test (as appropriate)[k]	(X)[e]						
Other assessments							
12-lead ECG[l]	(X)[e]	(X)[f]	Cycle 1, Day 15 only		X	(X)[g]	
MUGA or ECHO[m]	(X)[e]						
Tumor imaging[n]			standard of care	standard of care	X		
Adverse events[o]	X	X	X	X	X	X	
Concomitant medications/ treatments[p]	X	X	X	X	X	X	
Study treatment		X	X	X			
Study drug compliance				X	X		
Post study survival status[q]							X

EC = ethics committee; ECG = electrocardiogram; ECHO = echocardiogram; IRB = institutional review board; MUGA = multigated acquisition; QTc = corrected QT interval; (X) = if applicable.

a. Subjects receiving sunitinib with other anti-cancer therapies underwent additional safety assessments as required per standard of care for the other therapies. "Sunitinib experienced" refers to those subjects who received sunitinib in their previous sunitinib study.

b. "First exposure" refers to those subjects who did not receive sunitinib in their previous sunitinib study (eg, assigned to control arm in previous study). "Changing dosing regimen" refers to subjects who adopted a different sunitinib dosing regimen than received in previous study. Subjects having first sunitinib exposure or having a change in dosing regimen from previous study underwent assessments listed in this column according to the schedule outlined in Table 2. After completion of the required number of cycles, the subjects followed the procedures listed under the "all other cycles" column.

c. All other cycles: for subjects on a dosing schedule with a cycle duration <4 weeks (eg, Schedule 2/1), visits were held on Day 1 of each odd number cycle (eg, 6 week intervals) for the first 48 weeks on study and thereafter, visits were on Day 1 of every fourth cycle (eg, 12-week intervals). For subjects on a dosing schedule with a cycle duration ≥4 weeks (eg, Schedules 2/2, 4/2 and continuous dosing), visits were on Day 1 of each cycle (eg, 4-6 week intervals) for the first 48 weeks on study and thereafter, visits were on Day 1 of every even number cycle (eg, 8-12 week intervals).

d. Post-treatment follow-up visit was 28 days after the last dose of sunitinib.

e. Physical examination/hematology/biochemistry/12-lead ECG: not required at Screening if these were done in the prior sunitinib protocol and were done within 42 days of Cycle 1, Day 1.

Table 1. Schedule of Activities

f. Physical examination/hematology/biochemistry/12-lead ECG: not required at Cycle 1, Day 1 if these were done within 7 days of Cycle 1, Day 1.

g. Post-treatment follow-up: physical examination, hematology, biochemistry, ECG to be repeated if necessary for follow-up of adverse events.

h. Hematology, biochemistry.

i. Urinalysis: first exposure: dipstick protein urinalysis at Screening, Day 1 of Cycle 2, as clinically indicated and at the end of treatment. If the results of the dipstick test indicated a ≥2+ proteinuria, then follow-up was performed with a quantitative urine protein analysis according to local standard practices. Sunitinib experienced: as clinically indicated and at the end of treatment. If the results of the dipstick test indicated a ≥2+ proteinuria, then follow-up was performed with a quantitative urine protein analysis according to local standard practices.

j. Coagulation: first exposure: to be assessed only at Screening and if clinically needed thereafter. Sunitinib experienced: if clinically needed.

k. Pregnancy test: additional testing was repeated as per the request from IRBs, ECs or if required by local regulations.

l. 12-lead ECG: three 12-lead ECGs were performed 2 minutes apart to determine the mean QTc interval. The ECGs were performed at the same time of the day (eg, morning) and time matched (±1 hour). If the mean QTc was prolonged (>500 msec), then the ECGs were read by a cardiologist at the clinical site for confirmation. ECGs were completed at the time of discontinuation of study treatment. Additional ECGs were performed as clinically indicated to include 2 weeks following intrasubject sunitinib dose adjustments.

m. MUGA or ECHO: collected at Screening if not performed in the prior sunitinib protocol then as clinically indicated thereafter for studies of sunitinib in subjects having breast cancer who had previously received treatment with anthracyclines. For France Only: required at Screening if not performed in the prior sunitinib protocol or if the subject received placebo assignment in the prior sunitinib protocol.

n. Tumor imaging: was performed according to local standard of care during treatment and again at treatment withdrawal if not performed within previous 12 weeks.

o. Adverse events: subjects were followed for adverse events during the study until at least 28 days after the last dose of sunitinib, or until all serious or study drug-related toxicities resolved or were determined as “chronic” or “stable,” whichever was later. Serious adverse events were monitored and reported from the time that the subject provided informed consent.

p. 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 after the last dose of study treatment.

q. Poststudy survival status: were to be performed only in subjects for which overall survival was a study endpoint in their prior protocol. Survival data were collected every 2 months until death or up to 2 years from the date of the last dose of sunitinib.

Table 2. Clinic Visit Days for Either First Exposure to Sunitinib or Change in Dosing Regimen From Prior Protocol

Cycle Day[a]	Schedule 2/1	Schedule 2/2	Schedule 4/1	Schedule 4/2	Continuous Schedule	Other Schedules With an Off-Treatment Period
Day 1	X	X	X	X	X	X
Day 15	X	X	X	X	X	X
Day 29	not applicable	not applicable	X	X	same as day 1 of next cycle	end of on-treatment period
Number of cycles	3	2	2	2	2	2
Total number of weeks	9	8	10	12	8	8-12

a. Cycle 1, Day 1 procedures are listed under "Start of Treatment" column in Table 1. All other clinic visits should follow the procedures listed under "First Exposure or Changing Dosing Regimen" column in Table 1.

Number of Subjects (Planned and Analyzed): The number of subjects planned for enrollment was not predetermined. A total of 123 subjects were assigned to study treatment. One subject was assigned to study treatment, but did not receive a dose of study treatment; hence, a total of 122 subjects were treated with study drug.

Of 123 subjects, 42 subjects were randomized in the US, 23 in Canada, 22 in Italy, 12 each in Germany and the UK, 7 in France, and 5 in Spain.

Diagnosis and Main Criteria for Inclusion: Males and females aged 18 years or older and who participated in a previous sunitinib protocol and judged as having the potential to derive clinical benefit by remaining on sunitinib after the prior protocol ended by Investigator were included in the study. Subjects with severe acute or chronic medical or psychiatric condition, or laboratory abnormality that might increase the risk associated with study participation or study drug administration, or might interfere with the interpretation of study results, and in the judgment of the Investigator made the subject inappropriate for entry into this study were excluded from the study.

Study Treatment: Sunitinib was supplied as hard gelatin capsules. Sunitinib was administered orally without regard to meals. Administration of the study drug was performed on an outpatient basis. All subjects received open-label sunitinib. In most cases, the starting dose for all dosing regimens except for continuous dosing was 50 mg once daily (QD). For continuous dosing, the starting dose was generally 37.5 mg QD. However, the initial starting dose for any dosing regimen was modified if decided after discussion with the Sponsor. The duration of sunitinib treatment cycles on study ranged from 3 weeks for Schedule 2/1 to 6 weeks for Schedule 4/2. For the purpose of this study, continuous dosing of sunitinib was expressed in 4 week cycles. Sunitinib was taken orally without regard to meals beginning on Cycle 1, Day 1 of the study. The start of the next cycle was delayed if additional time was required for the subject to recover from sunitinib-associated toxicity experienced during the previous cycle.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

- Overall survival (OS) (for individual subjects enrolling from protocols with an OS endpoint)

- Time to Tumor Progression (TTP) and/or Progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors [RECIST]) criteria (for individual subjects who previously participated in protocols which included objective response rate (ORR), TTP, and/or PFS as a study endpoint)

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

Safety Evaluations: Safety evaluations included clinical monitoring, clinical laboratory measurements, vital signs, electrocardiograms, physical examinations, and cardiac function

(multigated acquisition scan or echocardiogram), assessment of AEs, and laboratory abnormalities.

Statistical Methods:

Analysis Sets: The intent-to-treat (ITT) analysis set included all subjects enrolled in the study who received at least 1 dose of study medication. This analysis set was used for all planned analyses in the study.

Efficacy Analyses: Descriptive statistics for continuous variables included the mean, standard deviation (SD), median, minimum, and maximum values. For categorical variables, summary measures included the number and percentage of subjects in each category. Unless otherwise noted, Baseline was defined as the last observation prior to the first dose of study drug in the analyses. Tumor response data were not formally analyzed in this study. Individual subject outcomes contributed to conclusions to their prior studies or were summarized as individual experiences.

Safety Analyses: Safety data were summarized descriptively. The AE reporting period for this study began upon receiving the first dose of sunitinib. All AEs reported during the AE reporting period were considered as treatment-emergent AEs (TEAEs). A pre-existing condition that worsened in severity during the AE reporting period (at the time the subject provided informed consent, through and including 28 calendar days after the last administration of the investigational product for serious AEs (SAEs) and from the time the subject took at least 1 dose of study drug through the last subject visit for AEs) was also considered as a TEAE. All AEs were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. The severity of all AEs was coded by using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. Local laboratory data were converted to Standard International units prior to summarization.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition is provided in Table 3. A total of 123 subjects were assigned to sunitinib. One subject was assigned to study treatment, but did not receive a dose of study treatment in this study. A total of 122 subjects were treated and all discontinued from the study. The most common reason for study discontinuation was insufficient clinical response (54.9%).

Table 3. Subject Disposition

Number (%) of Subjects	Sunitinib
Assigned to study treatment	123
Treated	122 (99.2)
Discontinued[a]	122 (99.2)
Number of subjects discontinued	122
Subject died	9 (7.4)
Related to study drug	10 (8.2)
Adverse event	10 (8.2)
Not related to study drug	103 (84.4)
Adverse event	6 (4.9)
Insufficient clinical response	67 (54.9)
No longer willing to participate in study	8 (6.6)
Other	10 (8.2)
Study terminated by Sponsor	12 (9.8)

a. Discontinued status was attained from the subject summary – end of study page.

A summary of demographic characteristics is provided in Table 4. Half of the subjects were male (50.0%), with a mean age of 59.9 years of age (range, 25 to 86 years of age).

Table 4. Demographic Characteristics (ITT)

	Sunitinib (N=122)
Male, n (%)	61 (50.0)
Female, n (%)	61 (50.0)
Age (years), n (%)	
<18	0
18-44	12 (9.8)
45-64	66 (54.1)
≥65	44 (36.1)
Mean (SD)	59.9 (11.7)
Median	60.0
Range	25-86
Weight (kg)	
Mean (SD)	73.6 (15.7)
Median	72.4
Range	40.0-125.1

Race and height were not collected on the CRF.
CRF = case report form; ITT = intent-to-treat; N = total number of subjects; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy Results: Tumor response data were not formally analyzed in this study and no statistical analyses were provided for OS, TTP, and PFS. A summary of survival (studies with survival summary as the endpoint only) is provided in Table 5. Of the 94 subjects from studies with survival summary as the endpoint, a total of 19 (20.2%) were alive, 43 (45.7%) were dead, and 32 (34.0%) had unknown survival status.

Table 5. Summary of Survival (ITT)[a]

	Sunitinib (N=94) n (%)
Alive	19 (20.2)
Death	43 (45.7)
Unknown	32 (34.0)

One death was not associated with study disease (congestive heart failure).
Subjects from the previous sunitinib protocols were included.
ITT = intent-to-treat; N = total number of subjects; n = number of subjects with specified criteria.
a. Last survival status used.

Safety Results: An overview of all-causality and treatment-related TEAEs is provided in Table 6. A total of 97.5% of subjects had an AE and 86.1% of subjects had a treatment-related AE during the study. A total of 28.7% of subjects had an SAE and 8.2% of subjects had a treatment-related SAE during the study.

Table 6. Overview of Treatment-Emergent Adverse Events (All Causality and Treatment Related, All Cycles) – ITT Population

	All Causality Sunitinib (N=122)	Treatment Related Sunitinib (N=122)
Number of subjects evaluable for AEs	122	122
Number of AEs	1293	657
Number (%) of subjects with AEs	119 (97.5)	105 (86.1)
Number (%) of subjects with SAEs	35 (28.7)	10 (8.2)
Number (%) of subjects with Grade 3 or Grade 4 AEs	70 (57.4)	47 (38.5)
Number (%) of subjects with Grade 5 AEs	11 (9.0)	0
Number (%) of subjects discontinued due to AEs	25 (20.5)	11 (9.0)
Number (%) of subjects with dose reduced due to AEs	7 (5.7)	5 (4.1)
Number (%) of subjects with temporary discontinuation due to AEs	57 (46.7)	50 (41.0)

AEs and SAEs are not separated out.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs – according to the Investigator's assessment.
AE = adverse event; ITT = intent-to-treat; N = total number of subjects; SAE = serious adverse event.

Treatment-Emergent Adverse Events: Table 7 presents TEAEs reported by ≥5% ITT population during the study. The most common all-causality AEs were diarrhea, fatigue, nausea, neutropenia, and decreased appetite.

Table 7. Treatment-Emergent Adverse Events Reported by ≥5% Population (ITT)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib (N=122) n (%)
Total number of subjects evaluable for adverse events (N):	122
Number of subjects with adverse events	115 (94.3)
Blood and lymphatic system disorders	51 (41.8)
Anaemia	24 (19.7)
Leukopenia	7 (5.7)
Neutropenia	32 (26.2)
Thrombocytopenia	17 (13.9)
Eye disorders	7 (5.7)
Eyelid oedema	7 (5.7)
Gastrointestinal disorders	86 (70.5)
Abdominal pain	13 (10.7)
Abdominal pain upper	11 (9.0)
Constipation	23 (18.9)
Diarrhoea	49 (40.2)
Dyspepsia	13 (10.7)
Nausea	33 (27.0)
Stomatitis	12 (9.8)
Vomiting	22 (18.0)
General disorders and administration site conditions	72 (59.0)
Asthenia	13 (10.7)
Chest pain	7 (5.7)
Fatigue	36 (29.5)
Mucosal inflammation	15 (12.3)
Oedema peripheral	24 (19.7)
Pain	8 (6.6)
Pyrexia	15 (12.3)
Infections and infestations	14 (11.5)
Nasopharyngitis	7 (5.7)
Upper respiratory tract infection	9 (7.4)
Investigations	17 (13.9)
Blood creatinine increased	8 (6.6)
Weight decreased	10 (8.2)
Metabolism and nutrition disorders	32 (26.2)
Decreased appetite	27 (22.1)
Hypokalaemia	7 (5.7)
Musculoskeletal and connective tissue disorders	31 (25.4)
Arthralgia	8 (6.6)
Back pain	18 (14.8)
Pain in extremity	11 (9.0)
Nervous system disorders	32 (26.2)
Dizziness	10 (8.2)
Dysgeusia	12 (9.8)
Headache	20 (16.4)
Respiratory, thoracic and mediastinal disorders	38 (31.1)
Cough	13 (10.7)
Dyspnoea	19 (15.6)
Epistaxis	14 (11.5)
Skin and subcutaneous tissue disorders	40 (32.8)
Dry skin	11 (9.0)
Erythema	9 (7.4)
Palmar-plantar erythrodysaesthesia syndrome	20 (16.4)
Rash	9 (7.4)
Vascular disorders	16 (13.1)
Hypertension	16 (13.1)

Table 7. Treatment-Emergent Adverse Events Reported by ≥5% Population (ITT)

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib (N=122) n (%)

Subjects are only counted once per treatment for each row.
Percentages are based on the total number of subjects within treatment group.
MedDRA (v14.1) coding dictionary is applied.
ITT = intent-to-treat; MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = total number of subjects; n = number of subjects.

Treatment-Emergent Treatment-Related Adverse Events: Table 8 presents treatment-related TEAEs reported by ≥5% ITT population during the study. The most common treatment-related, TEAEs were diarrhea (31.1%), Neutropenia (25.4%), and fatigue (23.0%).

Table 8. Summary of Treatment-Emergent Treatment-Related Adverse Events Experienced by ≥5% of Subjects (All Cycles) – ITT Population

MedDRA (v14.1) Preferred Term	Sunitinib (N=122) n (%)
Any AE	105 (86.1)
Diarrhea	38 (31.1)
Neutropenia	31 (25.4)
Fatigue	28 (23.0)
Decreased appetite	22 (18.0)
Anemia	21 (17.2)
Nausea	21 (17.2)
Palmar-plantar erythrodysesthesia syndrome	20 (16.4)
Thrombocytopenia	16 (13.1)
Mucosal inflammation	15 (12.3)
Vomiting	14 (11.5)
Hypertension	13 (10.7)
Edema peripheral	13 (10.7)
Epistaxis	11 (9.0)
Dysgeusia	11 (9.0)
Asthenia	10 (8.2)
Stomatitis	10 (8.2)
Dry skin	10 (8.2)
Dyspepsia	9 (7.4)
Headache	8 (6.6)
Erythema	7 (5.7)
Rash	7 (5.7)

AEs and SAEs are not separated out.
Subjects were counted only once per treatment in each row.
AE = adverse event; ITT = intent-to-treat; MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = total number of subjects; n = number of subjects with adverse event; SAE = serious adverse event.

Grade 3, 4, and 5 Adverse Events: The most common Grade 3, 4, and 5 TEAEs were neutropenia (10.7%), fatigue (9.0%), back pain (7.4%), and disease progression (7.4%). The most common treatment-related Grade 3, 4, and 5 TEAEs were neutropenia (9.0%) and fatigue (8.2%).

Treatment-Emergent Serious Adverse Events: Table 9 presents treatment-emergent SAEs reported during the study by the ITT population. A total of 35 (28.7%) subjects experienced

a treatment-emergent SAE during the study. The most common treatment-emergent SAEs included disease progression (7.4%) and dehydration (3.3%).

Table 9. Treatment-Emergent Serious Adverse Events Reported During the Study - ITT Population

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib (N=122) n (%)
Total number of subjects evaluable for adverse events (N):	122
Number of subjects with serious adverse events	35 (28.7)
Blood and lymphatic system disorders	6 (4.9)
Anaemia	3 (2.5)
Febrile neutropenia	2 (1.6)
Neutropenia	1 (0.8)
Cardiac disorders	1 (0.8)
Congestive cardiomyopathy	1 (0.8)
Endocrine disorders	1 (0.8)
Hypothyroidism	1 (0.8)
Gastrointestinal disorders	10 (8.2)
Abdominal distension	1 (0.8)
Abdominal pain	1 (0.8)
Ascites	1 (0.8)
Gastrointestinal haemorrhage	1 (0.8)
Haematemesis	1 (0.8)
Melaena	3 (2.5)
Nausea	1 (0.8)
Rectal haemorrhage	2 (1.6)
Small intestinal obstruction	2 (1.6)
Vomiting	2 (1.6)
General disorders and administration site conditions	13 (10.7)
Chest pain	1 (0.8)
Condition aggravated	1 (0.8)
Disease progression	9 (7.4)
Gait disturbance	1 (0.8)
Oedema peripheral	1 (0.8)
Hepatobiliary disorders	3 (2.5)
Cholangitis	1 (0.8)
Cholecystitis	2 (1.6)
Infections and infestations	5 (4.1)
Appendicitis perforated	1 (0.8)
Biliary sepsis	1 (0.8)
Catheter site infection	1 (0.8)
Gastroenteritis	2 (1.6)
Pneumonia	1 (0.8)
Urinary tract infection	1 (0.8)
Injury, poisoning and procedural complications	2 (1.6)
Fall	2 (1.6)
Metabolism and nutrition disorders	5 (4.1)
Dehydration	4 (3.3)
Hypoglycaemia	1 (0.8)
Musculoskeletal and connective tissue disorders	4 (3.3)
Back pain	3 (2.5)
Pain in extremity	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)
Lip and/or oral cavity cancer	1 (0.8)
Nervous system disorders	2 (1.6)
Cerebral haemorrhage	1 (0.8)
Headache	1 (0.8)
Psychiatric disorders	1 (0.8)
Confusional state	1 (0.8)
Renal and urinary disorders	2 (1.6)
Haematuria	1 (0.8)
Renal failure	1 (0.8)

Table 9. Treatment-Emergent Serious Adverse Events Reported During the Study - ITT Population

System Organ Class MedDRA (v14.1) Preferred Term	Sunitinib (N=122) n (%)
Respiratory, thoracic and mediastinal disorders	6 (4.9)
Bronchiectasis	1 (0.8)
Dyspnoea	3 (2.5)
Pulmonary embolism	1 (0.8)
Respiratory distress	1 (0.8)
Vascular disorders	1 (0.8)
Hypertensive emergency	1 (0.8)

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
ITT = intent-to-treat; MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = total number of subjects; n = number of subjects with adverse event.

Treatment-Emergent Treatment-Related Serious Adverse Events: Table 10 presents treatment-emergent treatment-related SAEs reported during the study by the ITT population. A total of 10 (8.2%) subjects experienced treatment-related SAEs. The most common treatment-emergent treatment-related SAE was febrile neutropenia, experienced by 2 (1.6%) subjects.

Table 10. Treatment-Emergent Treatment-Related Serious Adverse Events Reported During the Study (ITT)

MedDRA (v14.1) Preferred Term	Sunitinib (N=122) n (%)
Any SAEs	10 (8.2)
Febrile neutropenia	2 (1.6)
Abdominal pain	1 (0.8)
Anaemia	1 (0.8)
Biliary sepsis	1 (0.8)
Cerebral haemorrhage	1 (0.8)
Confusional state	1 (0.8)
Dehydration	1 (0.8)
Dyspnoea	1 (0.8)
Gastroenteritis	1 (0.8)
Gastrointestinal haemorrhage	1 (0.8)
Headache	1 (0.8)
Hypothyroidism	1 (0.8)
Melaena	1 (0.8)
Pulmonary embolism	1 (0.8)
Vomiting	1 (0.8)

ITT = intent-to-treat; MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); N = total number of subjects; n = number of subjects with specified adverse event; SAE = serious adverse event.

Discontinuations due to Adverse Events: A total of 46.7% of subjects had a temporary discontinuation of study drug due to an AE and 41.0% of subjects had a temporary discontinuation of study drug due to a treatment-related AE. A total of 25 (20.5%) subjects permanently discontinued the study due to an AE and 11 (9.0%) subjects permanently discontinued the study due to a treatment-related AE.

Deaths: A summary of deaths is provided in Table 11. A total of 47 (38.5%) subjects died including 9 (7.4%) subjects who died within 28 days of the last dose of study drug and 38 (31.1%) subjects who died more than 28 days after the last dose of study drug. The most common reason for death was disease under study. None of the deaths were considered related to sunitinib.

Table 11. Summary of Deaths (ITT)

Number (%) of Subjects	Sunitinib (N=122) n (%)
Death from all causes	47 (38.5)
Within 28 days of last dose of study drug	9 (7.4)
More than 28 days after last dose of study drug	38 (31.1)

Death information was from subject summary and/or survival summary pages.
ITT = intent-to-treat; N = total number of subjects; n = number of subjects with specified criteria.

Other Safety Related Findings: The safety profile of sunitinib in this study was consistent with the known safety profile.

CONCLUSIONS:

- Sunitinib treatment was provided to subjects who participated in a previous sunitinib protocol.
- Sunitinib was generally well tolerated; 11 (9.0%) of the subjects discontinued the study due to a treatment-related AE. The types, frequencies, and seriousness of reported events were similar to the known safety profile of sunitinib.
- Of the 122 subjects (94 subjects were from studies with survival as an endpoint), 47 subjects died (43 subjects were from studies with survival as an endpoint), 56 subjects had unknown survival status (32 subjects were from studies with survival as an endpoint), and 19 subjects were still alive (all subjects were from studies with survival as an endpoint) as of 16 December 2011.