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

PROTOCOL NO.: A6181036

PROTOCOL TITLE: A Treatment Protocol for Patients With Gastrointestinal Stromal Tumor who Are Ineligible for Participation in Other SU011248 Protocols and Are Refractory to or Intolerant of Imatinib Mesylate

Study Centers: A total of 104 centers took part in the study and randomized subjects, 22 centers in the United States, 8 centers in Italy, 7 centers in Australia, 6 centers each in Canada and Spain, 4 centers each in Germany, Taiwan, and in the United Kingdom, 3 centers each in France, India and Turkey, 2 centers each in Austria, Belgium, Czech Republic, Denmark, Hong Kong, Israel, the Republic of Korea, Mexico, Netherlands, Singapore, and Thailand, 1 center each in Argentina, Chile, Colombia, Finland, Greece, Hungary, Norway, Poland, Slovakia, Sweden, Switzerland, and Venezuela.

Study Initiation and Final Completion Dates: 13 September 2004 to 31 August 2011

Phase of Development: Not applicable

Study Objectives: The primary objective was to provide access to sunitinib treatment for subjects with gastrointestinal stromal tumor (GIST) given the following conditions:

- Subjects had received treatment with imatinib mesylate and had developed resistance or intolerance.
- Subjects had, in the judgment of the Investigator, the potential to derive clinical benefit from treatment with sunitinib.
- Subjects were ineligible for participation in ongoing sunitinib clinical studies (if any Phase 1, 2, or 3 sunitinib protocols for subjects having GIST were open to enrollment at the institution).

METHODS

Study Design: This study was an open-label "treatment use" protocol for subjects with imatinib refractory or intolerant GIST 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. Disease assessments for tumor response and progression was performed as per local standard of care of GIST. Minimal disease evaluation data (best response and date of progression) was collected.

Subjects continued to access sunitinib malate on this study as long as there was evidence of disease control in the judgment of the Investigator. Survival beyond participation in the study was monitored for up to 2 years from the date of the last dose of sunitinib malate.

Assessments and procedures were performed as outlined in Table 1.

Table 1. Schedule of Events

Parameters	Screen	Cycle 1 Treatment			Cycle 2		Cycles ≥3	End of Treatment/ Withdrawal	Post-Treatment[a]	Survival Follow-Up
	Days –45 to 1	Day 1 –1/+0	Day 14[b] –3/+3	Day 28 or End of Dosing –3/+3	Day 1 –1/+0	Day 28 or End of Dosing –3/+3	Day 1 –1/+0			
Informed consent	X									
Eligibility[c]	X									
Medical history	X									
Physical examination[d]	X	(X)[d]			X		X	X	(X)[d]	
Laboratory studies										
Pregnancy test[e]	X									
Hematology[d]	X	(X)[d]	(X)[b]	X	X	X	X	X	(X)[d]	
Biochemistry[d]	X	(X)[d]	(X)[b]	X	X	X through Cycle 3	X	X	(X)[d]	
Urinalysis[d]	X	(X)[d]					(X)	X	(X)[d]	
Registration[f]	X									
Other assessments										
12-lead ECG[g]	X[g]	(X)[g]		X[g]				X[g]	(X)[g]	
Disease assessment	X					X Standard of care	X Standard of care			
Adverse events[h]	X	X	X	X	X	X	X	X	X	
Concomitant medications/ treatments[i]	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[j]										X

(X) - if applicable; X→ - start and continue treatment → - continue treatment →X - stop treatment.
ECG = Electrocardiogram GIST = Gastrointestinal stromal tumor; IEC = independent ethics committee; IRB = institutional review board; QTc = Corrected QT (interval); screen = screening.

Table 1. Schedule of Events

a. Approximately 28 days post the last dose of study treatment.
b. This visit could be handled by telephone contact unless otherwise required on a country basis (eg, France). If a site visit was performed, hematology and biochemistry were performed.
c. Including ineligibility for other sunitinib Protocols: If any Phase 1, 2 or 3 sunitinib protocols for subjects having GIST were open to enrollment at the institution, subjects had to be declared ineligible before being considered for participation in this study.
d. Physical examination at Day 1, Cycle 1 was not required if done within the 45-day screening period.
Hematology/biochemistry/urinalysis was not required at Day 1, Cycle 1 if this was done within 7 days of Day 1. Both were to be performed at the post-treatment assessment if withdrawal was due to toxicity. Dipstick for, protein, glucose, ketones, blood and leukocyte at Screening, then as clinically indicated thereafter. 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 to be performed with a quantitative urine protein analysis according to local standard practices.
e. Performed within 21 days prior to the first dose of sunitinib for women of reproductive potential. Pregnancy tests may also have been repeated as per request of IEC/IRBs or if required by local regulations, eg, Austria.
f. Subject number and registration approval were obtained by faxing a completed eligibility-screening checklist to the Sponsor or designee. Subjects were to be registered within 7 days of Day 1, Cycle 1.
g. Three (3) 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 had to be completed at the time of discontinuation of study treatment. Additional ECGs were performed as clinically indicated, including 2 weeks following intrasubject sunitinib dose adjustments.
h. 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 to be “chronic” or “stable”, whichever was later. Serious adverse events were monitored and reported from the time that the subject provided informed consent. The assessment scheduled for the middle of the first cycle could have been accomplished through telephone contact unless otherwise required on a country basis (eg, France).
i. Concomitant medications and treatments were recorded from 28 days before the start of study treatment, during the study, and up to 28 days after the last dose of study treatment.
j. Follow-up survival information was collected by clinic visit or telephone contact every 2 months for up to 2 years from the date of last dose of sunitinib.

Number of Subjects (Planned and Analyzed): Due to the nature of the study the number of subjects to be enrolled was not predetermined; up to 1500 subjects could have been enrolled. A total of 1131 subjects were actually enrolled in the study; of these subjects, 1124 (99.4%) received at least 1 dose of sunitinib and qualified for the intent to treat (ITT) population.

Diagnosis and Main Criteria for Inclusion: Male or female subjects 18 years of age with histopathologically proven malignant GIST that was not amenable to standard therapy with curative intent, had undergone screening, and were found to be ineligible for participation in ongoing sunitinib clinical studies. Subjects judged to have potential to derive clinical benefit from sunitinib treatment by the treating Physician; or failed prior treatment with imatinib mesylate, defined as either progression of disease or significant toxicity during treatment with imatinib mesylate that precluded further treatment; with resolution of all acute toxicities of prior therapies and with adequate organ function as defined for the study.

Exclusion Criteria: Subjects with symptomatic congestive heart failure, myocardial infarction, or coronary artery bypass graft in the last 6 months, ongoing severe or unstable angina or any unstable arrhythmia requiring medication. Subjects with symptomatic central nervous system metastases; serious acute or chronic illness; current treatment on another clinical trial; pregnant or breastfeeding.

Study Treatment: Sunitinib was provided in hard gelatin capsules in 12.5, 25, and 50 mg dose strengths. Bottles containing 30 capsules with the correct capsule strength were dispensed to the subject at the start of each treatment cycle.

Sunitinib was self-administered orally on Schedule 4/2 (4 weeks of daily dosing followed by 2 weeks off-treatment in repeated 6 week cycles). The starting dose was to be 50 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 subject's dosing regimen schedule to continuous daily dosing (CDD). Cycles changed from 6 to 4 weeks in duration on the CDD regimen. For subjects on the CDD regimen, the typical starting dose was 37.5 mg once daily. 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 dose could escalate to 50 mg daily.

Efficacy Endpoints:

The primary objective was to provide access to sunitinib treatment for subjects with GIST without formal hypothesis testing. In addition, the following clinical endpoints were evaluated:

- Safety profile of sunitinib.
- Overall Survival (OS).

- Time to tumor progression (TTP).
- Objective response rate (ORR).

Safety Evaluations: Safety evaluations included adverse events (AEs) (from the first day of treatment to 28 days after the last dose of study drug); clinical laboratory tests (hematology and serum chemistry); electrocardiogram; vital signs; and eastern cooperative oncology group performance status. Also, a serum or urine pregnancy test, for females of child-bearing potential, was performed at Screening and thereafter as required by local national guidelines or institutional review board/independent ethics committee request.

Statistical Methods: Due to the nature of this study, no inferential analyses were planned, and no hypotheses were tested. However, objective response (per Investigator assessment), TTP, and OS 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). The data set for safety analysis was the safety population, which also included all subjects who enrolled in the study and received at least 1 dose of study medication. The ITT and safety populations were identical.

The ORR was defined as the number and percent of subjects with a confirmed response (complete or partial response) according to Response Evaluation Criteria in Solid Tumors and was provided along with the corresponding exact 95% 2-sided confidence interval (CI) using standard methods based on the binomial distribution.

Estimates of TTP and OS from the Kaplan-Meier product limit algorithm were presented. This algorithm was applied to derive the median event time and a CI for the median. The CI was 2-sided, had a stated coverage probability of 95%, and was calculated using normal approximation methods for fixed sample, single-stage design. If the number of events was small, thereby limiting use of the Kaplan-Meier method to provide reliable information, then descriptive statistics or listings were planned. Summaries of TTP and OS were presented in months overall.

RESULTS

Subject Disposition and Demography: A total of 1131 subjects were enrolled in the study; of these subjects, 1124 (99.4%) received at least 1 dose of sunitinib and qualified for the ITT population.

All 1124 ITT subjects discontinued treatment; 719 subjects (64.0%) discontinued because of lack of efficacy (disease progression), 186 (16.5%) withdrew consent, 169 subjects (15.0%) discontinued because of AEs (based on the end-of-study report form), 23 subjects (2.0%) discontinued at the Sponsor's discretion, 12 subjects (1.1%) completed treatment as allowed by the protocol, 8 subjects (0.7%) discontinued because of protocol deviations, and 7 subjects (0.6%) were lost to follow-up.

Most subjects in the ITT population were White (858 subjects, 76.3%) and 452 subjects (40.2%) were female. Eight (8) subjects were <18 years old (ages 16 [4 subjects] and 10, 11, 14, and 17 [each 1 subject] years). Demography is presented in Table 2.

Table 2. Summary of Demographic and Baseline Characteristics (ITT Population)

Variable	Sunitinib (N=1124)
Age (years)	
Mean (Std)	57.9 (13.79)
Median	59
(Min,Max)	(10, 92)
Age (years) [n (%)]	
<59 years	553 (49.2)
≥59 years	571 (50.8)
Sex [n (%)]	
Male	672 (59.8)
Female	452 (40.2)
ECOG [n (%)]	
0	420 (37.4)
1	521 (46.4)
2	135 (12.0)
3	33 (2.9)
4	5 (0.4)
Missing	10 (0.9)

% = (n/N)*100.
ECOG = eastern cooperative oncology group; ITT = intent-to-treat; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects with pre-specified criteria; Std = standard.

Efficacy Results:

Objective Response Rate: In the analysis of ORR, 88 subjects had a confirmed tumor response (complete response [CR] or partial response [PR]); the overall ORR was 7.8%, with a 95% CI of 6.3% to 9.6%. Six hundred thirty-nine (639) subjects (56.9% overall) had a best response of stable disease (SD). Overall, 509 subjects (45.3%) remained on study with SD or better for more than 6 months. ORR is presented in Table 3.

Table 3. Summary of Best Overall Tumor Response (ITT Population[a])

Variable	Sunitinib (N=1124)
Best overall tumor response (n [%])[a]	
Complete response	10 (0.9)
Partial response	78 (6.9)
Stable disease	639 (56.9)
Progressive disease	237 (21.1)
Not evaluable	2 (0.2)
Missing	158 (14.1)
Overall confirmed objective response (CR + PR) (n [%])	88 (7.8)
95% Exact CI (%)[b]	(6.3, 9.6)
Duration of clinical benefit response rate (CR, PR, SD)[c]	
≤6 Months	218 (19.4)
>6 Months	509 (45.3)

% = (n/N)*100.
CI = confidence interval; CR = complete response; ITT = intent-to-treat; PR = partial response; n = number of subjects with specified criteria; N = total number of subjects; SD = stable disease.

a. Only tumor assessment data on or before the last dose of study drug + 28 days were included in the analysis of best overall tumor response.
b. Using exact method based on binomial distribution.
c. For subjects whose best overall tumor response was CR, PR or SD.

Time to Tumor Progression and Overall Survival:

Results for TTP and OS are summarized in Table 4.

Table 4. Summary of Primary Time-to-Event Analyses (Months; ITT Population)

Variable	Total (N=1124)
Time to tumor progression	
Subject progression status [n (%)]	
Progression[a]	420 (37.4)
No progression[a]	704 (62.6)
Time to tumor progression (months)	
Percentile (95% CI)[b]	
25%	3.6 (2.8, 4.4)
50% (Median)	8.3 (8.0, 9.4)
75%	18.9 (16.4, 20.4)
Overall survival	
Subject survival status [n (%)]	
Alive	404 (35.9)
Dead	720 (64.1)
Survival time (Months)	
Percentile (95% CI)[b]	
25%	7.2 (6.4, 8.1)
50% (Median)	16.6 (14.9, 18.0)
75%	36.3 (32.1, 46.8)

% = (n/N)*100, Month was calculated as days/30.4375.
CI = confidence interval; ITT = intent-to-treat; N = number of subject; n = number of subjects with prespecified criteria.
a. Subjects who were not known to have progressive disease within 28 days of their last dose of sunitinib were censored on the date they were last known to be without disease progression.
b. Kaplan-Meier estimates.

Safety Results: Table 5 is an overall summary of non-serious AEs experienced by ≥5% subjects.

Table 5. Summary of Non-Serious Adverse Events Experienced by ≥5% of Subjects by MedDRA System Organ Class and Preferred Term (ITT Population)

System Organ Class Preferred Term	Sunitinib (N=1124)	
	Number (%) of Subjects	Number of Events
Any non-serious AEs ≥5%	1073 (95.5)	22165
Blood and lymphatic system disorders	479 (42.6)	2853
Anaemia	259 (23.0)	715
Leukopenia	145 (12.9)	512
Neutropenia	209 (18.6)	870
Thrombocytopenia	219 (19.5)	756
Endocrine disorders	158 (14.1)	200
Hypothyroidism	158 (14.1)	200
Gastrointestinal disorders	911 (81.0)	6809
Abdominal distension	130 (11.6)	207
Abdominal pain	396 (35.2)	706
Abdominal pain upper	158 (14.1)	303
Constipation	253 (22.5)	428
Diarrhoea	532 (47.3)	1721
Dry mouth	95 (8.5)	157
Dyspepsia	204 (18.1)	345
Flatulence	81 (7.2)	127
Gastrooesophageal reflux disease	81 (7.2)	140
Nausea	402 (35.8)	931
Oral pain	101 (9.0)	227
Stomatitis	264 (23.5)	757
Vomiting	348 (31.0)	760
General disorders and administration site conditions	850 (75.6)	3508
Asthenia	182 (16.2)	460
Chest pain	57 (5.1)	80
Fatigue	549 (48.8)	1493
Mucosal inflammation	263 (23.4)	608
Oedema	61 (5.4)	75
Oedema peripheral	232 (20.6)	386
Pain	79 (7.0)	108
Pyrexia	203 (18.1)	298
Infections and infestations	127 (11.3)	178
Nasopharyngitis	65 (5.8)	94
Urinary tract infection	65 (5.8)	84
Investigations	90 (8.0)	107
Weight decreased	90 (8.0)	107
Metabolism and nutrition disorders	435 (38.7)	932
Decreased appetite	397 (35.3)	851
Hypokalaemia	62 (5.5)	81
Musculoskeletal and connective tissue disorders	427 (38.0)	1283
Arthralgia	118 (10.5)	226
Back pain	157 (14.0)	273
Muscle spasms	73 (6.5)	113
Musculoskeletal pain	75 (6.7)	94
Myalgia	94 (8.4)	183
Pain in extremity	186 (16.5)	394
Nervous system disorders	407 (36.2)	1051
Dizziness	119 (10.6)	195

Table 5. Summary of Non-Serious Adverse Events Experienced by ≥5% of Subjects by MedDRA System Organ Class and Preferred Term (ITT Population)

System Organ Class Preferred Term	Sunitinib (N=1124)	
	Number (%) of Subjects	Number of Events
Dysgeusia	186 (16.5)	379
Headache	231 (20.6)	477
Psychiatric disorders	120 (10.7)	177
Insomnia	120 (10.7)	177
Respiratory, thoracic and mediastinal disorders	361 (32.1)	706
Cough	155 (13.8)	229
Dyspnoea	148 (13.2)	195
Epistaxis	111 (9.9)	174
Oropharyngeal pain	71 (6.3)	108
Skin and subcutaneous tissue disorders	689 (61.3)	3767
Alopecia	88 (7.8)	103
Dry skin	95 (8.5)	130
Erythema	63 (5.6)	138
Hair colour changes	111 (9.9)	152
Palmar-plantar erythrodysaesthesia syndrome	362 (32.2)	1955
Pruritus	68 (6.0)	96
Rash	196 (17.4)	554
Skin discolouration	176 (15.7)	314
Skin exfoliation	61 (5.4)	92
Yellow skin	127 (11.3)	233
Vascular disorders	321 (28.6)	594
Hypertension	321 (28.6)	594

AEs are coded using MedDRA version 14.1.
% = (n/N)*100.
AE = adverse events; MedDRA = medical dictionary for regulatory activities; N = total number of subjects; n = number of subjects with specified event.

Treatment-related AEs experienced by ≥5% subjects are summarized in Table 6.

Table 6. Treatment-Emergent Treatment-Related Adverse Events Experienced by ≥5% Subjects (ITT Population)

MedDRA Preferred Term	Sunitinib (N=1124)
Any treatment-related AEs	1030 (91.6)
Fatigue	477 (42.4)
Diarrhoea	454 (40.4)
Palmar-plantar erythrodysesthesia syndrome	363 (32.3)
Nausea	327 (29.1)
Decreased appetite	302 (26.9)
Hypertension	288 (25.6)
Stomatitis	258 (23.0)
Mucosal inflammation	258 (23.0)
Vomiting	247 (22.0)
Thrombocytopenia	223 (19.8)
Neutropenia	212 (18.9)
Anaemia	181 (16.1)
Dysgeusia	180 (16.0)
Rash	175 (15.6)
Skin discoloration	173 (15.4)
Dyspepsia	145 (12.9)
Hypothyroidism	143 (12.7)
Leukopenia	138 (12.3)
Oedema peripheral	135 (12.0)
Asthenia	131 (11.7)
Yellow skin	125 (11.1)
Headache	123 (10.9)
Pain in extremity	121 (10.8)
Hair color changes	109 (9.7)
Abdominal pain	107 (9.5)
Constipation	104 (9.3)
Oral pain	96 (8.5)
Dry skin	82 (7.3)
Alopecia	81 (7.2)
Epistaxis	80 (7.1)
Dry mouth	78 (6.9)
Abdominal pain upper	67 (6.0)
Myalgia	65 (5.8)
Arthralgia	63 (5.6)
Skin exfoliation	58 (5.2)

AEs were coded using MedDRA version 14.1.
Non SAE/SAE results are not separated out.
AE = adverse events; MedDRA = medical dictionary for regulatory activities; N = total number of subjects; SAE = serious adverse event.

All serious adverse events (SAEs) are summarized in Table 7. Six hundred one (601) subjects (53.5%) experienced SAEs.

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Any SAEs	601 (53.5)	1669
Blood and lymphatic system disorders	85 (7.6)	121
Anaemia	49 (4.4)	66
Thrombocytopenia	22 (2.0)	27
Neutropenia	11 (1.0)	13
Febrile neutropenia	3 (0.3)	3
Pancytopenia	3 (0.3)	3
Disseminated intravascular coagulation	2 (0.2)	2
Leukopenia	2 (0.2)	2
Bone marrow failure	1 (0.1)	1
Coagulopathy	1 (0.1)	1
Haemolysis	1 (0.1)	1
Haemolytic anaemia	1 (0.1)	1
Lymphopenia	1 (0.1)	1
Cardiac disorders	41 (3.6)	49
Myocardial infarction	9 (0.8)	9
Cardiac failure	6 (0.5)	8
Cardiac failure congestive	6 (0.5)	6
Cardio—respiratory arrest	4 (0.4)	4
Cardiac arrest	3 (0.3)	3
Acute coronary syndrome	2 (0.2)	2
Atrial fibrillation	2 (0.2)	2
Myocardial ischaemia	2 (0.2)	2
Ventricular tachycardia	2 (0.2)	2
Arrhythmia	1 (0.1)	1
Arrhythmia supraventricular	1 (0.1)	1
Atrial flutter	1 (0.1)	1
Atrioventricular block	1 (0.1)	1
Atrioventricular block complete	1 (0.1)	1
Cardiac failure acute	1 (0.1)	1
Cardiogenic shock	1 (0.1)	1
Congestive cardiomyopathy	1 (0.1)	1
Intracardiac thrombus	1 (0.1)	1
Left ventricular dysfunction	1 (0.1)	1
Ventricular arrhythmia	1 (0.1)	1
Ear and labyrinth disorders	3 (0.3)	3
Vertigo	3 (0.3)	3
Endocrine disorders	8 (0.7)	9
Hypothyroidism	6 (0.5)	7
Inappropriate antidiuretic hormone secretion	1 (0.1)	1
Myxoedema	1 (0.1)	1
Eye disorders	1 (0.1)	2
Eye haemorrhage	1 (0.1)	1
Eye pain	1 (0.1)	1
Gastrointestinal disorders	262 (23.3)	442
Abdominal pain	67 (6.0)	80
Vomiting	49 (4.4)	53
Nausea	32 (2.8)	35
Gastrointestinal haemorrhage	24 (2.1)	28

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Intestinal obstruction	23 (2.0)	24
Ascites	22 (2.0)	35
Diarrhoea	21 (1.9)	22
Constipation	13 (1.2)	14
Abdominal distension	11 (1.0)	12
Abdominal pain upper	10 (0.9)	11
Rectal haemorrhage	9 (0.8)	10
Haematemesis	8 (0.7)	8
Small intestinal obstruction	8 (0.7)	8
Melaena	7 (0.6)	8
Ileus	5 (0.4)	6
Upper gastrointestinal haemorrhage	5 (0.4)	6
Dysphagia	4 (0.4)	4
Gastritis	4 (0.4)	4
Haematochezia	4 (0.4)	4
Peritoneal haemorrhage	4 (0.4)	4
Subileus	4 (0.4)	4
Enterocutaneous fistula	3 (0.3)	5
Gastric haemorrhage	3 (0.3)	3
Gastric ulcer	3 (0.3)	3
Gastrooesophageal reflux disease	3 (0.3)	3
Lower gastrointestinal haemorrhage	3 (0.3)	3
Obstruction gastric	3 (0.3)	3
Pancreatitis acute	3 (0.3)	4
Stomatitis	3 (0.3)	3
Anal fissure	2 (0.2)	2
Duodenal ulcer	2 (0.2)	2
Gastric ulcer haemorrhage	2 (0.2)	2
Gastrointestinal fistula	2 (0.2)	2
Intestinal perforation	2 (0.2)	3
Oesophagitis	2 (0.2)	2
Pancreatitis	2 (0.2)	2
Small intestinal perforation	2 (0.2)	2
Abdominal pain lower	1 (0.1)	1
Anal fistula	1 (0.1)	1
Duodenal perforation	1 (0.1)	1
Duodenal ulcer perforation	1 (0.1)	1
Enteritis	1 (0.1)	1
Faecaloma	1 (0.1)	1
Faeces discoloured	1 (0.1)	1
Haemorrhagic ascites	1 (0.1)	1
Haemorrhoidal haemorrhage	1 (0.1)	1
Ileal fistula	1 (0.1)	1
Impaired gastric emptying	1 (0.1)	1
Intestinal fistula	1 (0.1)	3
Intestinal ischaemia	1 (0.1)	1
Large intestine perforation	1 (0.1)	1
Malabsorption	1 (0.1)	1
Oesophageal ulcer	1 (0.1)	1

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
General disorders and administration site conditions	254 (22.6)	299
Disease progression	158 (14.1)	158
Pyrexia	40 (3.6)	48
Asthenia	17 (1.5)	20
General physical health deterioration	14 (1.2)	16
Fatigue	13 (1.2)	13
Chest pain	11 (1.0)	11
Oedema peripheral	8 (0.7)	8
Generalised oedema	3 (0.3)	3
Pain	3 (0.3)	3
Mucosal inflammation	2 (0.2)	2
Multi-organ failure	2 (0.2)	3
Performance status decreased	2 (0.2)	2
Adverse event	1 (0.1)	1
Chills	1 (0.1)	1
Condition aggravated	1 (0.1)	1
Death	1 (0.1)	1
Device dislocation	1 (0.1)	1
Face oedema	1 (0.1)	1
Impaired healing	1 (0.1)	2
Localised oedema	1 (0.1)	1
Obstruction	1 (0.1)	1
Sudden death	1 (0.1)	1
Ulcer haemorrhage	1 (0.1)	1
Hepatobiliary disorders	29 (2.6)	32
Hyperbilirubinaemia	5 (0.4)	5
Jaundice	4 (0.4)	4
Cholangitis	3 (0.3)	4
Hepatic failure	3 (0.3)	3
Cholecystitis	2 (0.2)	2
Cholecystitis acute	2 (0.2)	2
Cholelithiasis	2 (0.2)	2
Hepatotoxicity	2 (0.2)	2
Biliary fistula	1 (0.1)	1
Cholangitis acute	1 (0.1)	1
Hepatic function abnormal	1 (0.1)	1
Hepatitis	1 (0.1)	1
Hepatorenal failure	1 (0.1)	1
Ischaemic hepatitis	1 (0.1)	1
Liver disorder	1 (0.1)	1
Perihepatic discomfort	1 (0.1)	1
Immune system disorders	1 (0.1)	1
Hypersensitivity	1 (0.1)	1
Infections and infestations	124 (11.0)	166
Pneumonia	21 (1.9)	22
Sepsis	18 (1.6)	20
Urinary tract infection	10 (0.9)	13
Abdominal abscess	7 (0.6)	7
Septic shock	7 (0.6)	7

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Infection	6 (0.5)	6
Anal abscess	5 (0.4)	5
Bacteraemia	5 (0.4)	5
Urosepsis	5 (0.4)	5
Cellulitis	4 (0.4)	4
Liver abscess	4 (0.4)	5
Abdominal wall abscess	3 (0.3)	3
Bacterial sepsis	3 (0.3)	3
Device related infection	3 (0.3)	4
Gastroenteritis	3 (0.3)	3
Infectious peritonitis	3 (0.3)	3
Respiratory tract infection	3 (0.3)	4
Biliary sepsis	2 (0.2)	2
Bronchopneumonia	2 (0.2)	2
Clostridium difficile colitis	2 (0.2)	2
Staphylococcal infection	2 (0.2)	2
Abscess	1 (0.1)	2
Abscess limb	1 (0.1)	1
Acarodermatitis	1 (0.1)	1
Acute tonsillitis	1 (0.1)	1
Blister infected	1 (0.1)	1
Bronchitis	1 (0.1)	1
Bronchopulmonary aspergillosis	1 (0.1)	1
Device related sepsis	1 (0.1)	1
Diabetic gangrene	1 (0.1)	1
Diarrhoea infectious	1 (0.1)	1
Ear infection	1 (0.1)	1
Endocarditis	1 (0.1)	1
Enterococcal infection	1 (0.1)	1
Erysipelas	1 (0.1)	1
Escherichia bacteraemia	1 (0.1)	1
Escherichia sepsis	1 (0.1)	1
Haematoma infection	1 (0.1)	1
Hepatitis B	1 (0.1)	2
Influenza	1 (0.1)	1
Lobar pneumonia	1 (0.1)	1
Lower respiratory tract infection	1 (0.1)	1
Lower respiratory tract infection bacterial	1 (0.1)	1
Lung abscess	1 (0.1)	1
Meningitis	1 (0.1)	1
Meningitis listeria	1 (0.1)	1
Necrotising fasciitis	1 (0.1)	2
Neutropenic sepsis	1 (0.1)	1
Osteomyelitis	1 (0.1)	1
Peridiverticular abscess	1 (0.1)	1
Purulent discharge	1 (0.1)	1
Pyelonephritis	1 (0.1)	1
Pyonephrosis	1 (0.1)	2
Rectal abscess	1 (0.1)	1

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Sinobronchitis	1 (0.1)	1
Subdiaphragmatic abscess	1 (0.1)	1
Injury, poisoning and procedural complications	19 (1.7)	24
Fall	6 (0.5)	6
Cervical vertebral fracture	2 (0.2)	2
Post procedural haemorrhage	2 (0.2)	2
Transfusion reaction	2 (0.2)	2
Abdominal injury	1 (0.1)	1
Accidental overdose	1 (0.1)	1
Femur fracture	1 (0.1)	1
Gastrointestinal stoma complication	1 (0.1)	2
Incisional hernia	1 (0.1)	1
Lower limb fracture	1 (0.1)	1
Pelvic fracture	1 (0.1)	1
Post procedural discharge	1 (0.1)	1
Road traffic accident	1 (0.1)	1
Spinal compression fracture	1 (0.1)	1
Toxicity to various agents	1 (0.1)	1
Investigations	30 (2.7)	45
Blood creatinine increased	5 (0.4)	6
Haemoglobin decreased	5 (0.4)	6
Ammonia increased	3 (0.3)	3
Aspartate aminotransferase increased	3 (0.3)	5
Alanine aminotransferase increased	2 (0.2)	3
General physical condition abnormal	2 (0.2)	2
Transaminases increased	2 (0.2)	3
Aspiration bronchial	1 (0.1)	1
Blood bilirubin increased	1 (0.1)	3
Blood potassium increased	1 (0.1)	1
Blood urine present	1 (0.1)	1
C-reactive protein increased	1 (0.1)	1
Ejection fraction	1 (0.1)	1
Ejection fraction decreased	1 (0.1)	1
Electrocardiogram QT prolonged	1 (0.1)	1
Electrocardiogram ST-T segment abnormal	1 (0.1)	1
Haemoglobin	1 (0.1)	1
Heart rate irregular	1 (0.1)	1
International normalised ratio	1 (0.1)	1
Neutrophil count	1 (0.1)	1
Weight decreased	1 (0.1)	1
White blood cell count decreased	1 (0.1)	1
Metabolism and nutrition disorders	64 (5.7)	79
Dehydration	42 (3.7)	44
Decreased appetite	9 (0.8)	10
Hypoglycaemia	4 (0.4)	5
Hyperkalaemia	3 (0.3)	3
Malnutrition	3 (0.3)	3
Acidosis	2 (0.2)	2
Hypercalcaemia	2 (0.2)	2

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Hyponatraemia	2 (0.2)	2
Cachexia	1 (0.1)	1
Electrolyte imbalance	1 (0.1)	1
Enzyme abnormality	1 (0.1)	1
Failure to thrive	1 (0.1)	1
Hypokalaemia	1 (0.1)	1
Hypophagia	1 (0.1)	1
Ketoacidosis	1 (0.1)	2
Musculoskeletal and connective tissue disorders	15 (1.3)	17
Fistula	5 (0.4)	6
Myalgia	2 (0.2)	2
Neck pain	2 (0.2)	2
Pain in extremity	2 (0.2)	2
Back pain	1 (0.1)	1
Hypercreatinaemia	1 (0.1)	2
Muscular weakness	1 (0.1)	1
Rhabdomyolysis	1 (0.1)	1
Neoplasms benign, malignant and unspecified (cysts and polyps)	43 (3.8)	49
Tumour haemorrhage	15 (1.3)	18
Gastrointestinal stromal tumour	12 (1.1)	12
Infected neoplasm	2 (0.2)	2
Tumour pain	2 (0.2)	4
Cholesteatoma	1 (0.1)	1
Gastrointestinal neoplasm	1 (0.1)	1
Haemorrhagic tumour necrosis	1 (0.1)	1
Hepatic neoplasm malignant	1 (0.1)	2
Malignant ascites	1 (0.1)	1
Malignant melanoma	1 (0.1)	1
Metastases to liver	1 (0.1)	1
Myelodysplastic syndrome	1 (0.1)	1
Oncologic complication	1 (0.1)	1
Pituitary tumour benign	1 (0.1)	1
Tumour flare	1 (0.1)	1
Tumour perforation	1 (0.1)	1
Nervous system disorders	64 (5.7)	82
Convulsion	8 (0.7)	10
Headache	7 (0.6)	7
Cerebrovascular accident	6 (0.5)	6
Somnolence	5 (0.4)	5
Syncope	5 (0.4)	6
Coma	3 (0.3)	3
Dizziness	3 (0.3)	3
Encephalopathy	3 (0.3)	3
Hemiparesis	3 (0.3)	3
Hepatic encephalopathy	3 (0.3)	4
Transient ischaemic attack	3 (0.3)	3
Coma hepatic	2 (0.2)	2
Epilepsy	2 (0.2)	2

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Lethargy	2 (0.2)	2
Posterior reversible encephalopathy syndrome	2 (0.2)	3
Spinal cord compression	2 (0.2)	2
Tremor	2 (0.2)	2
Cerebral haemorrhage	1 (0.1)	1
Cerebral infarction	1 (0.1)	1
Dementia	1 (0.1)	1
Depressed level of consciousness	1 (0.1)	1
Disturbance in attention	1 (0.1)	1
Dyskinesia	1 (0.1)	1
Embolic stroke	1 (0.1)	1
Grand mal convulsion	1 (0.1)	1
Guillain-Barre syndrome	1 (0.1)	1
Haemorrhage intracranial	1 (0.1)	2
Hypoaesthesia	1 (0.1)	1
Migraine	1 (0.1)	1
Neurological symptom	1 (0.1)	1
Peripheral sensory neuropathy	1 (0.1)	1
Subarachnoid haemorrhage	1 (0.1)	1
Psychiatric disorders	22 (2.0)	28
Confusional state	8 (0.7)	10
Mental status changes	5 (0.4)	7
Depression	3 (0.3)	3
Abnormal behaviour	1 (0.1)	1
Alcohol abuse	1 (0.1)	1
Alcoholic psychosis	1 (0.1)	1
Delirium	1 (0.1)	1
Disorientation	1 (0.1)	1
Hallucination	1 (0.1)	1
Mental disorder	1 (0.1)	1
Personality change	1 (0.1)	1
Renal and urinary disorders	43 (3.8)	51
Renal failure	15 (1.3)	16
Renal failure acute	7 (0.6)	7
Urinary retention	6 (0.5)	6
Azotaemia	4 (0.4)	4
Haematuria	3 (0.3)	4
Hydronephrosis	3 (0.3)	4
Nephrolithiasis	2 (0.2)	3
Calculus ureteric	1 (0.1)	1
Dysuria	1 (0.1)	1
Renal impairment	1 (0.1)	1
Ureteric obstruction	1 (0.1)	2
Urinary bladder haemorrhage	1 (0.1)	1
Vesical fistula	1 (0.1)	1
Reproductive system and breast disorders	3 (0.3)	3
Benign prostatic hyperplasia	1 (0.1)	1
Prostatic haemorrhage	1 (0.1)	1
Vaginal haemorrhage	1 (0.1)	1

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events
Respiratory, thoracic and mediastinal disorders	71 (6.3)	87
Dyspnoea	28 (2.5)	30
Pleural effusion	15 (1.3)	17
Pulmonary embolism	11 (1.0)	11
Pneumothorax	7 (0.6)	8
Respiratory failure	7 (0.6)	7
Pulmonary oedema	3 (0.3)	3
Epistaxis	2 (0.2)	2
Acute respiratory failure	1 (0.1)	1
Cough	1 (0.1)	1
Haemoptysis	1 (0.1)	1
Haemothorax	1 (0.1)	1
Hyperventilation	1 (0.1)	1
Laryngeal oedema	1 (0.1)	1
Lung disorder	1 (0.1)	1
Non-cardiogenic pulmonary oedema	1 (0.1)	1
Sputum discoloured	1 (0.1)	1
Skin and subcutaneous tissue disorders	12 (1.1)	17
Palmar-plantar erythrodysaesthesia syndrome	4 (0.4)	6
Rash	4 (0.4)	4
Skin ulcer	3 (0.3)	5
Stevens—Johnson syndrome	1 (0.1)	1
Subcutaneous emphysema	1 (0.1)	1
Surgical and medical procedures	4 (0.4)	4
Abdominal operation	1 (0.1)	1
Elective surgery	1 (0.1)	1
Gastrectomy	1 (0.1)	1
Gastrointestinal tube removal	1 (0.1)	1
Vascular disorders	54 (4.8)	59
Hypertension	17 (1.5)	19
Deep vein thrombosis	10 (0.9)	11
Hypotension	7 (0.6)	7
Haemorrhage	6 (0.5)	6
Circulatory collapse	3 (0.3)	3
Embolism	2 (0.2)	2
Hypertensive crisis	1 (0.1)	1
Lymphoedema	1 (0.1)	1
Orthostatic hypotension	1 (0.1)	1
Peripheral arterial occlusive disease	1 (0.1)	1
Peripheral ischaemia	1 (0.1)	1
Shock haemorrhagic	1 (0.1)	1
Thrombosis	1 (0.1)	1
Varicose ulceration	1 (0.1)	1
Vascular compression	1 (0.1)	1
Vena cava thrombosis	1 (0.1)	1
Venous thrombosis limb	1 (0.1)	1

% = (n/N)*100.
Adverse events are coded using MedDRA version 14.1.
ITT = intent-to-treat; MedDRA = medical dictionary for regulatory activities; N = total number of subjects;

Table 7. Summary of Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124) Number (%) of Subjects	Sunitinib (N=1124) Number of Events

n = number of subjects with specified event; SAE = serious adverse events.

Treatment-related SAEs are summarized in Table 8. A total of 247 (22.0%) subjects experienced SAEs considered related to the study drug. The most common treatment-related SAEs were anemia and vomiting (each 24 subjects, 2.1%), thrombocytopenia (19 subjects, 1.7%), nausea (16 subjects, 1.4%), hypertension (15 subjects, 1.3%), abdominal pain, diarrhea, and dehydration (each 13 subjects, 1.2%), and asthenia (11 subjects, 1.0%).

Table 8. Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124)	
	Number (%) of Subjects	Number of Events
Any treatment-related SAEs	247 (22.0)	491
Blood and lymphatic system disorders	56 (5.0)	79
Anemia	24 (2.1)	32
Thrombocytopenia	19 (1.7)	23
Neutropenia	10 (0.9)	12
Febrile neutropenia	3 (0.3)	3
Pancytopenia	3 (0.3)	3
Bone marrow failure	1 (0.1)	1
Coagulopathy	1 (0.1)	1
Disseminated intravascular coagulation	1 (0.1)	1
Haemolysis	1 (0.1)	1
Leukopenia	1 (0.1)	1
Lymphopenia	1 (0.1)	1
Cardiac disorders	24 (2.1)	28
Cardiac failure	6 (0.5)	8
Cardiac failure congestive	6 (0.5)	6
Myocardial infarction	4 (0.4)	4
Myocardial ischaemia	2 (0.2)	2
Atrial flutter	1 (0.1)	1
Cardiac arrest	1 (0.1)	1
Cardiac failure acute	1 (0.1)	1
Congestive cardiomyopathy	1 (0.1)	1
Intracardiac thrombus	1 (0.1)	1
Left ventricular dysfunction	1 (0.1)	1
Ventricular arrhythmia	1 (0.1)	1
Ventricular tachycardia	1 (0.1)	1
Ear and labyrinth disorders	2 (0.2)	2
Vertigo	2 (0.2)	2
Endocrine disorders	7 (0.6)	8
Hypothyroidism	6 (0.5)	7
Myxoedema	1 (0.1)	1
Gastrointestinal disorders	84 (7.5)	133
Vomiting	24 (2.1)	27
Nausea	16 (1.4)	18
Abdominal pain	13 (1.2)	13
Diarrhoea	13 (1.2)	14
Gastrointestinal haemorrhage	7 (0.6)	8
Haematemesis	5 (0.4)	5
Ascites	4 (0.4)	6
Melaena	4 (0.4)	5
Rectal haemorrhage	4 (0.4)	4
Stomatitis	3 (0.3)	3
Upper gastrointestinal haemorrhage	3 (0.3)	3
Abdominal distension	2 (0.2)	3
Haematochezia	2 (0.2)	2
Intestinal obstruction	2 (0.2)	2
Pancreatitis acute	2 (0.2)	3
Peritoneal haemorrhage	2 (0.2)	2
Anal fissure	1 (0.1)	1

Table 8. Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124)	
	Number (%) of Subjects	Number of Events
Anal fistula	1 (0.1)	1
Constipation	1 (0.1)	1
Duodenal ulcer	1 (0.1)	1
Dysphagia	1 (0.1)	1
Faeces discoloured	1 (0.1)	1
Gastric haemorrhage	1 (0.1)	1
Gastric ulcer	1 (0.1)	1
Gastric ulcer haemorrhage	1 (0.1)	1
Gastritis	1 (0.1)	1
Gastrooesophageal reflux disease	1 (0.1)	1
Haemorrhagic ascites	1 (0.1)	1
Intestinal perforation	1 (0.1)	2
Lower gastrointestinal haemorrhage	1 (0.1)	1
General disorders and administration site conditions	39 (3.5)	44
Asthenia	11 (1.0)	11
Fatigue	10 (0.9)	10
Pyrexia	5 (0.4)	6
Chest pain	2 (0.2)	2
Disease progression	2 (0.2)	2
Mucosal inflammation	2 (0.2)	2
Death	1 (0.1)	1
Face oedema	1 (0.1)	1
General physical health deterioration	1 (0.1)	1
Generalised oedema	1 (0.1)	1
Impaired healing	1 (0.1)	2
Localised oedema	1 (0.1)	1
Multi-organ failure	1 (0.1)	1
Oedema peripheral	1 (0.1)	1
Performance status decreased	1 (0.1)	1
Ulcer haemorrhage	1 (0.1)	1
Hepatobiliary disorders	8 (0.7)	8
Hepatic failure	2 (0.2)	2
Hepatotoxicity	2 (0.2)	2
Hyperbilirubinaemia	2 (0.2)	2
Jaundice	1 (0.1)	1
Liver disorder	1 (0.1)	1
Immune system disorders	1 (0.1)	1
Hypersensitivity	1 (0.1)	1
Infections and infestations	18 (1.6)	21
Abdominal wall abscess	2 (0.2)	2
Cellulitis	2 (0.2)	2
Infection	2 (0.2)	2
Pneumonia	2 (0.2)	3
Abdominal abscess	1 (0.1)	1
Abscess	1 (0.1)	1
Anal abscess	1 (0.1)	1
Hepatitis B	1 (0.1)	2
Liver abscess	1 (0.1)	1
Neutropenic sepsis	1 (0.1)	1

Table 8. Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124)	
	Number (%) of Subjects	Number of Events
Peridiverticular abscess	1 (0.1)	1
Respiratory tract infection	1 (0.1)	1
Sepsis	1 (0.1)	1
Urinary tract infection	1 (0.1)	1
Urosepsis	1 (0.1)	1
Injury, poisoning and procedural complications	1 (0.1)	1
Fall	1 (0.1)	1
Investigations	9 (0.8)	12
Aspartate aminotransferase increased	2 (0.2)	2
Alanine aminotransferase increased	1 (0.1)	1
Ammonia increased	1 (0.1)	1
Blood potassium increased	1 (0.1)	1
Ejection fraction	1 (0.1)	1
Electrocardiogram QT prolonged	1 (0.1)	1
Haemoglobin decreased	1 (0.1)	1
Heart rate irregular	1 (0.1)	1
International normalised ratio	1 (0.1)	1
Neutrophil count	1 (0.1)	1
White blood cell count decreased	1 (0.1)	1
Metabolism and nutrition disorders	21 (1.9)	25
Dehydration	13 (1.2)	13
Decreased appetite	5 (0.4)	6
Hyperkalaemia	2 (0.2)	2
Hypoglycaemia	2 (0.2)	2
Enzyme abnormality	1 (0.1)	1
Hypophagia	1 (0.1)	1
Musculoskeletal and connective tissue disorders	4 (0.4)	5
Hypercreatinaemia	1 (0.1)	2
Myalgia	1 (0.1)	1
Pain in extremity	1 (0.1)	1
Rhabdomyolysis	1 (0.1)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.6)	8
Tumour haemorrhage	5 (0.4)	6
Haemorrhagic tumour necrosis	1 (0.1)	1
Myelodysplastic syndrome	1 (0.1)	1
Nervous system disorders	28 (2.5)	37
Headache	6 (0.5)	6
Convulsion	5 (0.4)	6
Syncope	3 (0.3)	3
Cerebrovascular accident	2 (0.2)	2
Hemiparesis	2 (0.2)	2
Cerebral infarction	1 (0.1)	1
Depressed level of consciousness	1 (0.1)	1
Dizziness	1 (0.1)	1
Embolic stroke	1 (0.1)	1
Encephalopathy	1 (0.1)	1
Epilepsy	1 (0.1)	1
Guillain—Barre syndrome	1 (0.1)	1

Table 8. Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term (ITT Population)

MedDRA System Organ Class Preferred Term	Sunitinib (N=1124)	
	Number (%) of Subjects	Number of Events
Hemorrhage intracranial	1 (0.1)	2
Hepatic encephalopathy	1 (0.1)	1
Hypoesthesia	1 (0.1)	1
Lethargy	1 (0.1)	1
Neurological symptom	1 (0.1)	1
Posterior reversible encephalopathy syndrome	1 (0.1)	2
Somnolence	1 (0.1)	1
Subarachnoid haemorrhage	1 (0.1)	1
Transient ischaemic attack	1 (0.1)	1
Psychiatric disorders	9 (0.8)	10
Confusional state	5 (0.4)	5
Mental status changes	2 (0.2)	2
Abnormal behaviour	1 (0.1)	1
Depression	1 (0.1)	1
Disorientation	1 (0.1)	1
Renal and urinary disorders	7 (0.6)	8
Azotemia	3 (0.3)	3
Renal failure	2 (0.2)	2
Renal failure acute	1 (0.1)	1
Renal impairment	1 (0.1)	1
Urinary bladder hemorrhage	1 (0.1)	1
Reproductive system and breast disorders	1 (0.1)	1
Vaginal hemorrhage	1 (0.1)	1
Respiratory, thoracic and mediastinal disorders	19 (1.7)	21
Dyspnoea	9 (0.8)	9
Pleural effusion	6 (0.5)	6
Pulmonary embolism	3 (0.3)	3
Cough	1 (0.1)	1
Haemothorax	1 (0.1)	1
Pulmonary oedema	1 (0.1)	1
Skin and subcutaneous tissue disorders	10 (0.9)	13
Palmar-plantar erythrodysaesthesia syndrome	4 (0.4)	6
Rash	4 (0.4)	4
Skin ulcer	2 (0.2)	2
Stevens-Johnson syndrome	1 (0.1)	1
Vascular disorders	25 (2.2)	26
Hypertension	15 (1.3)	16
Hemorrhage	3 (0.3)	3
Deep vein thrombosis	2 (0.2)	2
Circulatory collapse	1 (0.1)	1
Embolism	1 (0.1)	1
Hypertensive crisis	1 (0.1)	1
Peripheral arterial occlusive disease	1 (0.1)	1
Peripheral ischemia	1 (0.1)	1

% = (n/N)*100.
Adverse events are coded using MedDRA version 14.1.
ITT = intent-to-treat; MedDRA = medical dictionary for regulatory activities; N = total number of subjects; n = number of subjects with specified event; SAE = serious adverse event.

Discontinuations Due to AEs: Eighty-three (83) subjects (7.4%) discontinued because of AEs considered by the Investigator to be possibly related to treatment. Treatment-related AEs leading to treatment discontinuation included asthenia, cardiac failure, and diarrhea (each 4 subjects); cardiac failure congestive, palmar-plantar erythrodysesthesia syndrome, and thrombocytopenia (each 3 subjects); cerebrovascular accident, dyspnea, fatigue, hepatotoxicity, and tumor hemorrhage (each 2 subjects); and abdominal pain, anemia, anal abscess, blood creatinine increased, cardiac arrest, cardiac failure acute, cerebral infarction, cerebrovascular accident, cognitive disorder, constipation, convulsion, deep vein thrombosis, dehydration, depressed level of consciousness, disease progression, ejection fraction, embolism, gastrointestinal hemorrhage, general physical health deterioration, Guillain-Barre syndrome, hemolysis, hemorrhagic ascites, hepatic failure, hyperbilirubinemia, hypertension, hyperuricemia, hypothyroidism, impaired healing, leukopenia, mucosal inflammation, multiorgan failure, myocardial infarction, nausea, nephropathy toxic, esophagitis, pain, pancytopenia, performance status decreased, peridiverticular abscess, peripheral arterial occlusive disease, peritoneal hemorrhage, pleural effusion, posterior reversible encephalopathy, pulmonary embolism, rectal hemorrhage, renal impairment, sepsis, skin toxicity, skin ulcer, transient ischaemic attack, ventricular tachycardia, vertigo, and vomiting (each 1 subject).

Deaths: A summary of deaths is provided in Table 9. Two hundred thirty-five (235) subjects (20.9%) died on study. Of the deaths, 197 deaths (17.5% subjects) were considered to be due to disease progression or to events secondary to disease progression. Seventeen (17) subjects (1.5%) died because of AEs considered to be possibly related to study treatment, including 7 subjects who died because of AEs related both to disease progression and possibly study drug. Possibly treatment-related deaths included embolic/hemorrhagic events (6 subjects; embolism, gastrointestinal bleeding, hemorrhage from ruptured liver tumor, intraperitoneal bleeding, rectal hemorrhage, and pulmonary embolism), cardiotoxicity (3 subjects; heart failure [2 subjects] and myocardial infarction), hepatic toxicities (2 subjects; hepatic failure and hepatic toxicity), disease progression (2 subjects; disease progression and disease progression/performance status decreased [these events were listed on the report form as related to the study drug and related to both the study drug and study disease]), and hemolysis, multi-organ failure, sepsis, and death (each 1 subject). Twenty-four (24) subjects (2.1%) died because of AEs related to neither the study drug nor the study disease, including 4 who died from unknown causes.

Table 9. Summary of Deaths (ITT Population)

Variable	Sunitinib (N=1124) n (%)
Subjects who died	722 (64.2)
On-study deaths[a]	235 (20.9)
Abdominal pain	1 (0.1)
Accidental fall	1 (0.1)
Bacteremia	1 (0.1)
Bronchoaspiration	1 (0.1)
Car accident	1 (0.1)
Cardiac arrest	1 (0.1)
Cardio-pulmonary arrest	1 (0.1)
Cardiorespiratory arrest	1 (0.1)
Clinical progression of disease	1 (0.1)
Colon perforation	1 (0.1)
Coma	2 (0.2)
Coma for liver dysfunction	1 (0.1)
Death due to disease progression	5 (0.4)
Death due to progression of disease	1 (0.1)
Death of unknown cause	1 (0.1)
Deterioration of GIST	2 (0.2)
Deterioration of study disease	1 (0.1)
Deterioration of the general condition	1 (0.1)
Deterioration of the general status	1 (0.1)
Disease progression	83 (7.4)
Disease progression resulting in death	1 (0.1)
Disease progression, performance status decreased	1 (0.1)
Disease progression-worsened	1 (0.1)
Dyspnea	1 (0.1)
Electrolytic imbalance	1 (0.1)
Embolism	1 (0.1)
Fatal disease progression	1 (0.1)
Fever	1 (0.1)
Gastrointestinal bleeding	2 (0.2)
General deterioration	2 (0.2)
General health deterioration	1 (0.1)
General physical health deterioration	2 (0.2)
General status impairment	1 (0.1)
GIST progression	2 (0.2)
Heart attack	1 (0.1)
Heart failure	1 (0.1)
Hemolysis	1 (0.1)
Hemorrhage from ruptured liver tumor	1 (0.1)
Hepatic failure	1 (0.1)
Hepatic toxicity	1 (0.1)
Ileus	1 (0.1)
Intraperitoneal bleeding	1 (0.1)
Listeria meningitis	1 (0.1)
Liver and kidney failure	1 (0.1)
Massive GI bleed	1 (0.1)
Mulit organic failure	1 (0.1)
Multiorganic failure	1 (0.1)
Multiple organ failure	1 (0.1)

Table 9. Summary of Deaths (ITT Population)

Variable	Sunitinib (N=1124) n (%)
Myocardial infarction	1 (0.1)
Pneumonia	2 (0.2)
Possible cerebral vascular accident	1 (0.1)
Progress disease	1 (0.1)
Progression disease	4 (0.4)
Progression of disease	6 (0.5)
Progression of disease under study	1 (0.1)
Progression of GIST	5 (0.4)
Progression of underlying malignancy (GIST)	1 (0.1)
Progressive disease	45 (4.0)
Pulmonary embolism	2 (0.2)
Pulmonary oedema	1 (0.1)
Pylorus ulcer	1 (0.1)
Respiratory failure	3 (0.3)
Sepsis	4 (0.4)
Septic shock	3 (0.3)
Septicaemia	2 (0.2)
Sudden death	1 (0.1)
Suspected cerebral bleeding	1 (0.1)
Tumor bleeding	2 (0.2)
UNK acute event	1 (0.1)
Unknown	1 (0.1)
Upper GI bleeding	1 (0.1)
Urosepsis	2 (0.2)
Worsening of disease under study	1 (0.1)
Worsening of gastrointestinal tumour	1 (0.1)
Worsening of GIST	1 (0.1)
Follow-up deaths[b]	487 (43.3)
Abdominal membrane bleeding (peritoneum)	1 (0.1)
Advanced parkinson's disease issues	1 (0.1)
Bowel obstruction	1 (0.1)
Bronchial-Ca	1 (0.1)
Cardiac arrest	1 (0.1)
Chronic renal failure	1 (0.1)
Death due to disease progression	1 (0.1)
Diabetic gangreene and cardiopulmonary failure	1 (0.1)
Disease progression	7 (0.6)
Hepatic encephalopathy	1 (0.1)
Hypothyroidism	1 (0.1)
Intracerebral bleeding	1 (0.1)
Intracranial bleed	1 (0.1)
lung abscess	1 (0.1)
Lung cancer	1 (0.1)
Multiorgan failure	1 (0.1)
Multiple organ failure	1 (0.1)
Pneumonia	1 (0.1)
Pneumonia secondary to lung metsfrom GIST. contributing factor: bacteremia	1 (0.1)
Post-operative complications	1 (0.1)
Progression of disease	1 (0.1)
Progressive disease	430 (38.3)

Table 9. Summary of Deaths (ITT Population)

Variable	Sunitinib (N=1124) n (%)
Rectal bleeding	1 (0.1)
Relapse of cardiac insufficiency	1 (0.1)
Renal failure	2 (0.2)
Respiratory tract infection	1 (0.1)
Sepsis	2 (0.2)
Septic shock	2 (0.2)
Unknown	7 (0.6)
Unknown cause	1 (0.1)
Unknown reason	1 (0.1)
Yellow pigmentation of skin	1 (0.1)
Cause of death missing	11 (1.0)

% = (n/N)*100.
Ca = carcinoma; GI = gastrointestinal bleeding; GIST = gastrointestinal stromal tumor; ITT = intent-to-treat; N = total number of subjects; n = number of subjects with specified event; UNK = unknown.

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. Survival beyond participation in the study was monitored for up to 2 years from the date of the last dose of sunitinib.

CONCLUSIONS:

Access to sunitinib was provided to a substantial number of subjects with imatinib refractory/intolerant metastatic GIST who did not qualify for other sunitinib studies; 1124 subjects had received sunitinib through this protocol, with treatment periods extending up to more than 6 years. The safety profile was generally acceptable, clinically manageable, and similar to what has been previously reported for sunitinib in the prescribing information for Sutent®. Though results should be interpreted with caution, evidence of antitumor efficacy was observed in this treatment use protocol, with an ORR of 7.8%, median TTP of 8.3 months, and median OS of 16.6 months in this highly varied population of subjects with imatinib refractory or intolerant GIST.