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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00137449

PROTOCOL NO.: A6181047

PROTOCOL TITLE: A Phase 2 Efficacy and Safety Study of SU011248 Administered in a Continuous Daily Regimen in Patients with Advanced Gastrointestinal Stromal Tumor.

Study Centers: 2 Centers in France, 1 Center in the United States, and 1 Center in Italy.

Study Initiation and Completion Dates: 23 September 2005 to 10 April 2008

Phase of Development: Phase 2

Study Objectives: The primary objective of this study was to evaluate the antitumor activity of SU011248 (sunitinib malate) in advanced imatinib mesylate-resistant gastrointestinal stromal tumor (GIST) when administered on a continuous daily dosing (CDD) schedule.

The secondary objectives were the following: to evaluate the safety and tolerability of sunitinib malate administered in a continuous treatment regimen; to evaluate the tolerability of sunitinib malate administered in the morning versus in the evening prior to sleep; to determine SU011248 and SU012662 trough concentrations (C_{trough}) for the evaluation of steady-state pharmacokinetics; to explore the correlations of potential biomarkers with clinical outcomes; to assess patient-reported outcomes (PROs).

METHODS

Study Design: This study was an open-label, uncontrolled, multi-center, Phase 2 clinical trial of sunitinib malate on a CDD schedule in subjects with advanced imatinib mesylate-resistant or intolerant GIST. Subjects received a once daily dose of sunitinib malate in either the morning or in the evening. The study was to consist of a screening visit within 21 days of the first dose, followed by 28-day treatment cycles for up to 1 year (in the absence of any withdrawal criteria). Subjects experiencing benefit after completing 1 year of treatment were offered continued access to sunitinib malate on a separate protocol. The maximum duration of treatment under this protocol was 24 cycles or 2 years of treatment. Subjects were required to attend visits at the study center on Day 1 of each treatment cycle, and Day 15 of treatment cycles 1 and 2. In cycles after cycle 2, a visit was required on

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Day 15 only in the case of dose escalation to 50 mg daily. A Day 15 visit was then required for a further 2 cycles.

Number of Subjects (Planned and Analyzed): Out of 61 planned subjects, 60 were treated in the study; 30 subjects (50.0%) with sunitinib malate in the morning (AM Cohort), and 30 subjects (50.0%) with sunitinib malate in the evening (PM Cohort).

Diagnosis and Main Criteria for Inclusion: Subjects of 18 years of age or older were required to have histopathologically proven diagnosis of malignant GIST that was not amenable to standard therapy and failed prior treatment with imatinib mesylate, defined either by progression of disease (according to the Response Evaluation Criteria in Solid Tumors [RECIST] or the World Health Organization criteria) or by significant toxicity during treatment with imatinib mesylate that precluded further treatment. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate vital organ function were also required for eligibility.

Study Treatment: Subjects received sunitinib malate at a starting dose of 37.5 mg/day in repeated 4-week cycles. Doses could be increased to 50 mg daily. Reduction to 25 mg daily could occur in the event of sunitinib malate-related toxicity. Intra-subject re-escalation back to the previous dose level was permitted in the absence of grade ≥2 hematologic or grade ≥1 non-hematologic sunitinib malate-related toxicity in the previous cycle.

Efficacy Evaluations: The determination of antitumor efficacy was based on objective tumor assessments made according to RECIST. Clinical benefit response (CBR) was the primary efficacy endpoint. CBR rate was defined as the percent of subjects with confirmed complete resonse (CR), partial response (PR) or (stable disease [SD] for at least 24 weeks) on the study according to RECIST, relative to the total population of subjects enrolled who received at least 1 dose of study treatment, had measurable disease at baseline, and the correct histological cancer type.

Secondary efficacy endpoints included the following: objective response rate (ORR), duration of response (DR), time to tumor progression (TTP), progression-free survival (PFS), overall survival (OS), one-year survival, and PROs (measured by the Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-Fatigue] Scale and the EuroQol 5-dimensional [EQ-5D] self-report questionnaire).

Pharmacokinetic and Pharmacodynamic Evaluations: Blood samples for determination of the trough concentrations (pre-dose) of SU011248 and its active metabolite, SU012662, were obtained for subjects randomized to morning dosing only and analyzed using a validated method. Pre-dose and trough concentrations of SU011248, SU012662, and total drug (SU011248 + SU012662) were summarized by cycle and study day using descriptive statistics.

Blood samples from the same subset of subjects were collected at the same time points as trough drug samples and were analyzed by ELISA for relevant soluble proteins associated with angiogenesis, sunitinib malate mechanism of action, or tumor proliferation (these were from a panel of proteins that includes soluble vascular endothelial growth factor [sVEGF],

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soluble vascular endothelial growth factor receptor [sVEGFR-2 and 3], and soluble tryosine kinase receptor [sKIT]). No blood concentration or protein samples were collected from subjects receiving sunitinib malate in the evening. Pre-study and on-study tumor biopsy samples were optional. Pre-dose plasma samples for analysis of soluble protein biomarkers were collected before dosing on Day 1 of each cycle and at the end-of-treatment visit for subjects randomized to morning dosing only. At each time point, one 10 mL blood sample was collected in a (green-top) tube with heparin.

Safety Evaluations: Safety evaluations included adverse events (AEs) (AEs were reported from the screening day until at least 28 days after the last dose of study treatment); clinical laboratory tests (hematology and serum chemistry [performed at: screening, Day 1 and Day 15 of each cycle, and withdrawal]), thyroid testing (performed at: screening, Day 1 of each cycle, and withdrawal), and pregnancy testing (performed at: screening); electrocardiogram (ECG) (performed at: screening, Day 1 of cycle 2 and withdrawal); vital signs and ECOG performance status (performed at screening, Day 1 of each cycle, and withdrawal). Clinical laboratory tests and thyroid testing may have been performed, and vital signs and ECOG performance status may have been measured 28 days after the last dose of study treatment.

Statistical Methods: The planned sample size of 61 subjects was associated with at least 90% power to detect a difference between the null hypothesis of ≤20% CBR rate and the alternative hypothesis of ≥35% CBR rate using a 1-sided, binomial hypothesis test with a significance level of 0.10. The set of subjects analyzed for CBR, ORR, DR, TTP, and PFS was all enrolled subjects who had the correct histological cancer type, measurable disease at baseline, and received at least 1 dose of sunitinib malate. The number and percent of subjects achieving CBR (CR, PR or [SD for at least 24 weeks]) and objective response (CR or PR) were summarized along with exact 95% confidence intervals (CIs); time-to-event endpoints (DR, TTP, PFS, and OS) were summarized using Kaplan-Meier methods. PRO endpoints (FACIT-Fatigue and EQ-5D) were scored and assessed as recommended in their respective users' manuals. Safety analyses were descriptive and included summaries of AEs, serious adverse events (SAEs), deaths, discontinuations due to AEs, clinical laboratory findings, ECG, and vital signs results. AEs were also summarized by National Cancer Institute Common Terminology Criteria for AEs (CTCAE version 3.0) severity grade, and laboratory results were summarized as shifts from baseline in CTCAE grade.

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RESULTS

Subject Disposition and Demography: Subject disposition and subjects analyzed are shown in Table S1. Of the 26 subjects that completed the study, 24 continued treatment on a continuation protocol (10 subjects to A6181030 and 14 subjects to A6181078), and 2 subjects remained on the current protocol.

Table S1. Subject Disposition and Subjects Analyzed

	Sunitinib malate Total (n%)
Planned	61
Treated	60
Completed[a]	26 (43.3)
Discontinued due to:	
Lack of efficacy	21 (35.0)
AEs	4 (6.7)
Death	7 (11.7)
Other	2 (3.3)
ITT population	60 (100.0)
PK population	30 (50.0)

[a] The protocol defined subjects who completed 1 year of treatment as having completed the study.
n= Number of subjects with observations or included in the analysis populations.
AEs= Adverse events.
ITT= Intention to treat.
PK= Pharmacokinetic.

Overall, 60 subjects began treatment at a dose of 37.5 mg daily in cycle 1. Fifty-nine subjects (98.3%) continued to additional treatment cycles; 1 subject discontinued before entering cycle 2 because of lack of efficacy. Forty-two subjects (70.0%) entered cycle 7 of treatment, completing more than approximately 6 months of treatment. The maximum duration of treatment under this protocol was 24 cycles or 2 years of treatment.

All subjects had failed prior treatment with imatinib mesylate due to either progression (57 subjects, 95.0%) or intolerance (3 subjects, 5.0%). The population was primarily white (80.0%), over half the subjects were female (53.3%), and the median age was 58.5 years. The overall median time since initial diagnosis was 188.4 weeks, and the most common metastatic sites included the liver (71.7%), peritoneum (55.0%), and lung (10.0%). In general, subjects were able to maintain compliance with the daily dosing schedule. Forty-six subjects (76.6%) had at least 1 dosing interruption, with the AM Cohort (27 subjects, 90%) having a higher frequency of dosing interruptions than the PM Cohort (19 subjects, 63.3%). The median percentage of days with dosing interruption was 3.8%.

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Efficacy Results: A summary of CBR rate and ORR is shown in Table S2. The CBR (CR + PR + [SD for at least 24 weeks]) rate was 53.3% (32 of 60 subjects; 95% CI: 40.0%, 66.3%), including 8 partial responders, and 24 subjects with SD ≥24 weeks. Because 17 subjects had CR, PR, or (SD ≥24 weeks) (protocol-defined threshold), the null hypothesis that the CBR rate was ≤20% was rejected at an alpha level of 10%. The overall confirmed ORR was 13.3% (8 of 60 subjects; 95% CI: 5.9%, 24.6%).

Table S2. Summary of Clinical Benefit Response Rate and Objective Response Rate By Cohort (Derived Assessment)

Variable	AM Cohort (N=30)	PM Cohort (N=30)	Total (N=60)
Baseline disease assessments	30	30	60
Measurable disease at baseline	30	30	60
Measurable disease at baseline, correct histological type[a]	30	30	60
Best confirmed response [n(%)]			
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (PR)	3 (10.0)	5 (16.7)	8 (13.3)
Stable disease (SD)	20 (66.7)	20 (66.7)	40 (66.7)
Progressive disease (PD)	2 (6.7)	4 (13.3)	6 (10.0)
Not evaluable (NE)	5 (16.7)	1 (3.3)	6 (10.0)
Clinical benefit response (CBR) rate [n(%)]			
CR+PR+(SD for 24 Weeks)	15 (50.0)	17 (56.7)	32 (53.3)
95% exact CI (%)	(31.3, 68.7)	(37.4, 74.5)	(40.0, 66.3)
Overall confirmed ORR [n(%)]	3 (10.0)	5 (16.7)	8 (13.3)
95% exact CI (%)[b]	(2.1, 26.5)	(5.6, 34.7)	(5.9, 24.6)
Duration of stable disease [n][c]			
≥12 weeks	19	14	33
≥24 weeks	12	12	24

[a] This value (N+) is the denominator for percentages in this table.
[b] Using exact method based on F distribution.
[c] Excludes subjects with a defined confirmed objective response.
n= Number of subjects with observations.
N= Number of subjects in the total population.
CI= Confidence interval.

The data for the other secondary endpoints are summarized in Table S3. Median PFS was 33.6 weeks (95% CI: 24.1, 49.0) and median TTP was 42.1 weeks (95% CI: 26.1, 65.9). Median DR for the 8 responders, based on descriptive statistics, was 33.9 weeks (range: 17.1 - 51.4). Five of the 8 responders were still ongoing at the time of analysis. The overall estimated probability of survival at 1 year was 69.7% (95% CI: 56.3, 79.7). Median OS was 107.1 weeks (95% CI: 72.1, Not Reached).

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Table S3. Summary of Time-to-Event Analyses (ITT) Population

Variable	AM Cohort (N=30)	PM Cohort (N=30)	Total (n=60)
Progression-free survival (PFS)			
Number of events [n(%)]a	18 (60.0)	20 (66.7)	38 (63.3)
Median[b] weeks (95% CI)	27.0 (22.0, 73.1)	35.1 (24.4, 51.6)	33.6 (24.1, 49.0)
Time-to-tumor progression (TTP)			
Number of events [n(%)]	12 (40.0)	17 (56.7)	29 (48.3)
Median[b] weeks (95% CI)	57.0 (24.1, 73.1)	42.1 (26.1, 65.9)	42.1 (26.1, 65.9)
Duration of response (DR)			
Number of responders [n (%)]	3 (10.0)	5 (16.7)	8 (13.3)
Number of events [n(%)][a,c]	0 (0.0)	3 (60.0)	3 (37.5)
Median[b] weeks (95% CI)	----	44.1 (17.1, NR)	44.1 (25.3, NR)
Overall survival (OS)			
Number of events [n(%)][a]	14 (46.7)	13 (43.3)	27 (45.0)
Median[b] weeks (95% CI)	107.1 (41.1, NR)	NR (68.1, NR)	107.1 (72.1, NR)
One-year survival rate (%)	60.0	79.7	69.7
95% CI	(40.5, 75.0)	(60.3, 90.3)	(56.3, 79.7)

[a] On study includes the 28-day follow-up period.
[b] Median PFS, TTP, DR, and OS analyses use Kaplan-Meier estimates with 95% CI calculated based on the method of Brookmeyer and Crowley, the missing values in DR and OS analyses are due to the small number of qualifying events available for Kaplan-Meier analysis.
[c] DR is calculated for the subgroup of subjects with a confirmed objective tumor response. Percentages for the number of events are based on the number of responders.
NR= Not reached, values could not be estimated at the time of analysis.
n= Number of subjects with observations.
N= Number of subjects in the total population.
CI= Confidence interval.

The overall FACIT-Fatigue scale score change from baseline did not exceed -4.0 for any time point at which results were available for ≥10 subjects. The maximum median increase in the EQ-5D overall health thermometer score (in the total group, for time points at which data were available for ≥10 subjects) was 18 points (cycle 14, Day 1). The rate of compliance for completing the questionnaire was highly variable throughout the study.

Pharmacokinetic and Pharmacodynamic Results: Following CDD of sunitinib malate, the mean trough plasma concentration values (Day 1 of cycles 2-13) for sunitinib malate, its metabolite, and total drug were within 26.30–41.87 ng/mL, 10.69–17.74 ng/mL, and 37.80-59.61 ng/mL , respectively. Dose-corrected (reference dose: 37.5 mg) trough values (Day 1 of cycles 2-13) for SU011248, its metabolite, and total drug were within 31.43-43.96 ng/mL, 13.06-18.97 ng/mL, and 45.01–62.76 ng/mL, respectively. Based on these values, steady state was reached within the first cycle. Dose-corrected trough values were relatively unchanged among cycles. Following CDD of sunitinib malate, there appeared to be no disproportionate accumulation of SU011248 and SU012662 throughout the study. Based on the dose-corrected trough values , the steady state pharmacokinetics of SU011248 and SU012662 after a CDD Schedule was generally similar to that after the 4/2 Schedule.

The effects of CDD of sunitinib malate on plasma levels of the target-related proteins VEGF, sVEGFR-2, sVEGFR-3, and sKIT were evaluated to investigate possible associations with

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clinical outcome. Plasma levels of VEGF increased, and plasma levels of sVEGFR-2, sVEGFR-3, and sKIT decreased in response to CDD with sunitinib malate. Unlike the cyclical changes in VEGF, sVEGFR-2, and sVEGFR-3 that were observed in previous studies of sunitinib malate, levels of these plasma proteins did not return towards baseline at any time during CDD. At cycles 6 and 7, Day 1, subjects with less than median sKIT ratios showed significantly prolonged OS compared to those with greater than median sKIT ratios (cycle 6 hazard ratio = 0.1316 [95% CI: 0.0274, 0.6324]; cycle 7 hazard ratio = 0.0731 [95% CI: 0.0137, 0.3904]).

Safety Results: The most common AEs were consistent with conditions associated with advanced GIST and with known toxicities of sunitinib malate, similar to events previously reported at an interim analysis of the Phase 3 clinical trial. Common AEs were generally gastrointestinal (diarrhea, abdominal pain, nausea, vomiting, abdominal pain upper, constipation, stomatitis), constitutional (asthenia, fatigue, anorexia, mucosal inflammation, pyrexia, headache), cutaneous (palmar-plantar erythrodysesthesia syndrome, hair color changes), or myelosuppressive (anemia, neutropenia, thrombocytopenia, epistaxis). Other common AEs were hypertension, back pain, edema peripheral, pain in extremity, and blood thyroid stimulating hormone increased. The majority of these AEs were grade 1 or 2 in severity and were adequately managed with standard treatment with or without dose interruption and/or reduction. Generally, more severe AEs were also similar to those that may be expected in a subject population with advanced GIST and the known grade 3-4 toxicities of sunitinib malate. A summary of the most common (occurring in ≥10% of subjects) is shown in Table S4.

Ten subjects (16.7%; 6 vs 4 subjects on the AM versus PM Cohorts, respectively) died on study (ie, after their first dose and within 28 days of their last dose of study treatment), and 17 subjects (28.3%; 8 vs 9 subjects) died during follow-up (>28 days after the last dose of study treatment). Seven of the 10 on-study deaths were considered unrelated to study treatment and were attributed to the underlying disease. One subject in the AM Cohort experienced grade 5, treatment-related septic shock. Two on-study deaths were not related to study treatment (one subject died of bilateral strokes during debulking surgery, and one subject died of an unknown cause). All deaths occurring during the follow-up period (off study treatment) were considered related to disease under study/disease progression.

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Table S4. Summary of the Most Common (≥10% Total Subjects) Adverse Events (ITT Population)

	AM Cohort (N=30)		PM Cohort (N=30)		Total (N=60)	
Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any adverse event	30 (100.0)	677	30 (100.0)	574	60 (100.0)	1251
Anemia	15 (50.0)	36	14 (46.7)	44	29 (48.3)	80
Diarrhea	17 (56.7)	55	10 (33.3)	31	27 (45.0)	86
Abdominal pain	11 (36.7)	15	13 (43.3)	16	24 (40.0)	31
Asthenia	13 (43.3)	36	10 (33.3)	38	23 (38.3)	74
Fatigue	12 (40.0)	23	10 (33.3)	20	22 (36.7)	43
Nausea	11 (36.7)	18	10 (33.3)	15	21 (35.0)	33
Vomiting	14 (46.7)	28	7 (23.3)	17	21 (35.0)	45
Hypertension	10 (33.3)	15	8 (26.7)	10	18 (30.0)	25
Neutropenia	9 (30.0)	30	9 (30.0)	42	18 (30.0)	72
Anorexia	8 (26.7)	11	7 (23.3)	8	15 (25.0)	19
Palmar-plantar erythrodysesthesia syndrome	8 (26.7)	12	7 (23.3)	14	15 (25.0)	26
Headache	8 (26.7)	9	6 (20.0)	14	14 (23.3)	23
Abdominal pain upper	5 (16.7)	10	8 (26.7)	12	13 (21.7)	22
Back Pain	7 (23.3)	9	6 (20.0)	9	13 (21.7)	18
Constipation	8 (26.7)	13	5 (16.7)	5	13 (21.7)	18
Hair color changes	7 (23.3)	8	6 (20.0)	7	13 (21.7)	15
Stomatitis	7 (23.3)	11	6 (20.0)	12	13 (21.7)	23
Thrombocytopenia	7 (23.3)	19	6 (20.0)	13	13 (21.7)	32
Epistaxis	7 (23.3)	7	5 (16.7)	5	12 (20.0)	12
Mucosal inflammation	3 (10.0)	7	8 (26.7)	19	11 (18.3)	26
Edema peripheral	8 (26.7)	9	3 (10.0)	3	11 (18.3)	12
Pain in extremity	8 (26.7)	9	2 (6.7)	2	10 (16.7)	11
Pyrexia	5 (16.7)	7	6 (20.0)	7	11 (18.3)	14
Blood TSH increased	5 (16.7)	6	4 (13.3)	5	9 (15.0)	11
Gastroesophageal reflux disease	4 (13.3)	5	4 (13.3)	4	8 (13.0)	9
Hypoalbuminemia	3 (10.0)	5	5 (16.7)	5	8 (13.0)	10
Hypothroidism	4 (13.3)	4	4 (13.3)	4	8 (13.0)	8
Rash	6 (20.0)	7	2 (6.7)	3	8 (13.0)	10
Arthralgia	5 (16.7)	9	2 (6.7)	2	7 (11.7)	11
Chills	3 (10.0)	3	4 (13.3)	4	7 (11.7)	7
Dyspnea	3 (10.0)	3	4 (13.3)	5	7 (11.7)	8
Muscle spasms	4 (13.3)	4	3 (10.0)	6	7 (11.7)	10
Dry skin	4 (13.3)	4	2 (6.7)	2	6 (10.0)	6
Eczema	1 (3.3)	1	5 (16.7)	7	6 (10.0)	8
Leukopenia	4 (13.3)	9	2 (6.7)	3	6 (10.0)	12
Weight decreased	2 (6.7)	2	4 (13.3)	5	6 (10.0)	7
Yellow skin	3 (10.0)	3	3 (10.0)	3	6 (10.0)	6

TSH= Thyroid stimulating hormone.
n= Number of subjects with observations.
N= Number of subjects in the total population.

Twenty-five subjects (41.7%) experienced a total of 68 SAEs, including 8 subjects (13.3%) who experienced 15 treatment-related SAEs. Most SAEs were experienced by 1 subject overall. Treatment-related SAEs experienced by more than 1 subject were vomiting and anemia. A summary of all SAEs is shown in Table S5.

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Table S5. Summary of All Serious Adverse Events (ITT Population)

	AM Cohort (N = 30)		PM Cohort (N = 30)		Total (N =60)	
Preferred Term	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any Adverse Event	13 (43.3)	40	12 (40.0)	28	25 (41.7)	68
Vomiting	4 (13.3)	4	1 (3.3)	1	5 (8.3)	5
Anemia	3 (10.0)	4	0 (0.0)	0	3 (5.0)	4
Diarrhea	3 (10.0)	4	0 (0.0)	0	3 (5.0)	4
Disease progression	1 (3.3)	1	3 (10.0)	3	4 (6.7)	4
Nausea	2 (6.7)	2	1 (3.3)	1	3 (5.0)	3
Asthenia	3 (10.0)	3	0 (0.0)	0	3 (5.0)	3
General physical health deterioration	3 (10.0)	4	0 (0.0)	0	3 (5.0)	4
Dehydration	1 (3.3)	1	1 (3.3)	2	2 (3.3)	3
Gastrointestinal hemorrhage	1 (3.3)	1	1 (3.3)	1	2 (3.3)	2
Wound infection	1 (3.3)	1	1 (3.3)	1	2 (3.3)	2
Pyrexia	0 (0.0)	0	2 (6.7)	2	2 (3.3)	2
Abdominal wall hemorrhage	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Gastrointestinal perforation	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Peritonitis	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Death	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Fatigue	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Hernia pain	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Septic shock	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Urinary tract infection staphylococcal	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Blood TSH increased	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Anorexia	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Cachexia	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Pain in extremity	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Syncope	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Confusional state	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Dyspnea	1 (3.3)	1	0 (0.0)	0	1 (1.7)	1
Abdominal pain	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Constipation	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Dental caries	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Intestinal obstruction	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Esophagitis hemorrhagic	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Pneumatosis intestinalis	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Chest pain	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Chills	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Catheter-related infection	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Emphysematous cystitis	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Pyelonephritis	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Sepsis	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Urinary tract infection	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Weight decreased	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Back pain	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Cerebrovascular accident	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1
Transient ischemic attack	0 (0.0)	0	1 (3.3)	1	1 (1.7)	1

TSH= Thyroid stimulating hormone.
n= Number of subjects with observations.
N= Number of subjects in the total population.

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Thirteen subjects (21.7%) experienced AEs for which the action taken was "drug permanently withdrawn". AEs that led to discontinuation of more than 1 subject were disease progression, general physical health deterioration, asthenia, and abdominal pain. The number of subjects who experienced grade 3 or 4 clinical laboratory abnormalities was generally low and similar to what might be expected in subjects with advanced GIST. Additional safety monitoring and ECGs did not reveal any unexpected toxicities of sunitinib malate. Evaluation of sunitinib malate tolerability on the AM versus PM Cohorts was based on predefined events of interest, including but not limited to: dose reduction due to AE(s), need for treatment rest, nausea grade ≥3, fatigue or asthenia grade ≥3, and hand and foot dermal effects grade ≥3. AEs that resulted in dose schedule modification included anemia, asthenia, neutropenia, and diarrhea, all grade ≥3. The only one of these AEs that was reported with a difference of ≥10% between the 2 cohorts was diarrhea (20.0% AM Cohort vs 3.3% PM Cohort). Overall, more subjects in the AM Cohort (27 subjects; 90.0%) had dosing interruptions due to an AE than in the PM Cohort (19 subjects; 63.3%). The only AE associated with dosing interruption at a differential frequency of at least 10% between cohorts was grade ≥3 diarrhea (16.7% vs 6.7%, on the AM vs PM Cohorts, respectively). The percentage of subjects experiencing AEs associated with dose reduction was the same in the AM and PM Cohorts (23.3%), and no AE associated with dose reduction was reported in more than 1 subject per cohort. The incidence of treatment-related SAEs was greater in the AM Cohort (6 subjects, 20.0%) than in the PM Cohort (2 subjects, 6.7%). SAEs that appeared to be more common in the AM Cohort than in the PM Cohort included vomiting, anemia, asthenia, diarrhea, and general physical health deterioration.

CONCLUSIONS: Sunitinib malate 37.5 mg on a CDD schedule demonstrated clinically relevant antitumor activity with overall CBR rate and ORR of 53.3% and 13.3%, respectively, in subjects with advanced imatinib mesylate-resistant or intolerant GIST.

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

Following CDD with sunitinib malate, the steady state SU011248 and SU012662 concentrations were reached within the first cycle without disproportionate accumulation of SU011248 and SU012662 throughout the study.

Reduction in plasma sKIT levels during continuous daily sunitinib malate dosing was associated with antitumor activity in GIST.

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

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