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

PROTOCOL NO.: A6181112

PROTOCOL TITLE: A Phase IIIb, Randomized, Active Controlled, Open-Label Study of Sunitinib (Sutent®) 37.5 mg Daily vs Imatinib Mesylate 800 mg Daily in the Treatment of Patients With Gastrointestinal Stromal Tumors (GIST) Who Have had Progressive Disease While on 400 mg Daily of Imatinib

Study Centers: A total of 20 centers took part in the study and enrolled subjects: 5 in the United Kingdom (UK), 3 each in Germany, Hong Kong, and Korea, and 2 each in Italy, Spain, and the United States (US).

Study Initiation Date and Final Completion Date: 06 June 2007 to 23 November 2009. The study was terminated prematurely.

Phase of Development: Phase 3b

Study Objectives:

Lead-In Safety Substudy (Phase 1): The objective of the lead-in Safety Substudy was to demonstrate that sunitinib 37.5 mg could safely be given 24 hours following a 400 mg dose of imatinib.

Main Study (Phase 3): Due to termination of the study, the objectives of the Main Study were amended from comparison between the 2 regimens to estimation of the treatment effect.

Primary Objective:

- To estimate the treatment effect on the progression-free survival (PFS) between sunitinib (37.5 mg daily) and imatinib 800 mg daily in subjects whose disease had progressed on imatinib 400 mg daily.

Secondary Objectives:

- To estimate the treatment effect on the objective response (OR) rates (ORR) between the 2 regimens;
- To estimate time-to-tumor response (TTR) for each of the 2 regimens;

- To estimate duration of response (DR) for each of the 2 regimens in responders;
- To estimate the treatment effect on time-to-treatment failure (TTF) between the 2 regimens;
- To estimate the treatment effect on overall survival (OS) between the 2 regimens;
- To assess pain relief/pain progression in the 2 regimens;
- To assess patient-reported outcomes (PROs);
- To evaluate safety and tolerability of the 2 drug regimens.

METHODS:

Study Design:

Lead-In Safety Substudy (Phase 1): A Safety Substudy was conducted at 1 study center. The purpose of the Substudy was to evaluate pharmacokinetics (PK) and treatment-related adverse events (AEs) in subjects taking a dose of sunitinib 24 hours after the last dose of imatinib. Six subjects were enrolled and assessed; all subjects in the Substudy were evaluated for AEs. Subjects were asked to take their last dose of imatinib in the morning on the day before coming to the clinic for the first dose of sunitinib. A dose of sunitinib (37.5 mg) was administered in the clinic approximately 24 hours after the last dose of imatinib (400 mg).

Seven days following the first dose of sunitinib, subjects were assessed for any adverse reactions that had occurred during the first week of treatment. If 2 or more of the 6 subjects presented with a Grade 3 or 4 treatment-related AE during the first week, an internal safety assessment committee was to be convened and the safety data reviewed. If there were no subjects or only 1 subject with a Grade 3 or 4 treatment-related adverse reaction in the first week, then the study was to proceed as planned. Following the treatment of the first 6 subjects (ie, 7 days of dosing), an additional 6 subjects were treated and assessed to provide additional AE, electrocardiogram (ECG), and PK data in subjects taking a dose of sunitinib 24 hours after a 400 mg dose of imatinib.

Subjects participating in the lead-in Safety Substudy were required to meet all inclusion/exclusion criteria for the Main Study.

Treatment in this study was planned to proceed until death, disease progression, or for a period of 1 year, whichever was earlier. Subjects participating in the lead-in Safety Substudy and still deriving clinical benefit from sunitinib after 1 year were allowed to proceed to the Main Study; these subjects were included in the analysis of safety in the Main Study, but not included in the analysis of efficacy.

Main Study (Phase 3): The Main Study was a multicenter, randomized (1:1), open-label, parallel arm, active-controlled, Phase 3b clinical study evaluating the efficacy and safety of single-agent sunitinib (37.5 mg continuous daily dosing) versus imatinib (800 mg daily) in

subjects with gastrointestinal stromal tumors (GIST) whose disease has progressed on 400 mg daily of imatinib.

Eligible subjects with GIST (N=200 planned subjects) were stratified by previous imatinib treatment status (less than 6 months of treatment with imatinib [“primary resistance”] versus 6 months or more of treatment with imatinib [“secondary resistance”]) and randomized to receive either open-label sunitinib (37.5 mg daily) or open-label imatinib (800 mg daily). The randomization was balanced by country/region.

Subjects were treated until disease progression, death, withdrawal from the study, or until the final analysis was performed, whichever was earlier. Subjects were followed for survival status for a maximum of 2 years from the time they were enrolled in the study, or up to 01 November 2009, whichever occurred first, regardless of whether they were still on study treatment. The original planned cutoff for the final analysis was when 93 events (progression of disease or death) had occurred; this cutoff was removed when the study was terminated for operational reasons.

This study was stopped prematurely on 18 June 2009 due to operational issues (ie, poor recruitment, lack of interest, and change of clinical practice) and not related to safety concerns.

The schedules of activities during the study (lead in Safety Substudy-Phase 1 and Main Study-Phase 3) are provided in Table 1 and Table 2.

Table 1. Schedule of Activities for Subjects in Safety Substudy

Protocol Activities and Forms to be Completed	Screening ≤14 Days Before Dosing	Treatment With Sunitinib[a]		
		Baseline (Day 1[b];–1/+0)	Day 7	Day 14
Informed consent[c]; medical/oncology history and demographics[d]	X			
Baseline signs and symptoms[e]		(X)		
Physical examination[f]	X	(X)		
Hematology[g,h]; blood chemistry[h,i]	X	(X)	X	X
Urinalysis[j]	X		X	X
Blood sample for plasma sunitinib and SU-012662 concentrations[k]		X; 6 hours postdose	X; predose	X; predose
Prothrombin time and partial thromboplastin time	X			
Thyroid function test[l]	X			
Pregnancy test[m]	(X)			
12-lead ECG[n]	X	X; 6 hours postdose	X; predose[n,o]	X, predose[n,o]
MUGA or echocardiogram to assess LVEF[p]	X			
Study treatment[q]		X	→X	→X
Contrast tumor imaging[r]	X			
ECOG PS[f], body weight, height, and vital signs measurement	X	(X)		X
Adverse events[s]	X	X	X	X
Study drug compliance[t]		X	X	X
Concomitant medications and treatments[u]	X	X	X	X

(X) = if clinically applicable; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition (scan); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; PS = performance status; QTc = corrected QT interval; TSH = thyroid-stimulating hormone; WBC = white blood cell.

a. During treatment, all assessments were performed before dosing with sunitinib, unless otherwise indicated.
b. Baseline (Day 1): hematology, ECOG PS, and physical examination were not required if an acceptable screening assessment was performed within 7 days before the start of treatment with sunitinib.
c. Informed consent was required to be obtained before undergoing any study specific procedures and may have occurred before the 14-day screening period.
d. Included oncologic history, demographics, history of other disease processes (active or resolved), and concomitant illnesses.
e. Subjects were asked about any signs or symptoms experienced within the past 14 days.
f. Performed during screening; performed at baseline, if applicable. Physical examination included examination of major body systems, height (at screening visit only), ECOG PS, body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate).
g. CBC, WBC with differential count, hemoglobin, and platelet count.
h. Samples were analyzed using local laboratories.
i. Total and indirect bilirubin, ALT, AST, alkaline phosphatase, amylase, lipase, total protein, albumin, globulin, sodium, potassium, chloride, magnesium, calcium, phosphorus, BUN, creatinine, uric acid, and glucose. Amylase and lipase at screening only.
j. For urinalysis, in cases of ≥2+ protein, a 24-hour urine to confirm NCI CTCAE was required; dose modification and interruption rules applied by grade for nonhematologic toxicity. Repeated as clinically required.
k. PK samples were to be obtained as soon as possible after ECG measurement.
l. Subsequent thyroid tests if clinically indicated (eg, fatigue of CTCAE Grade 3 or greater, abnormal TSH). Recommended follow-up based on institutional standard.

Table 1. Schedule of Activities for Subjects in Safety Substudy

m.	Pregnancy test (serum or urine) for women of reproductive potential; required to be tested within 7 days before the first treatment.
n.	A 12-lead ECG was performed at screening to determine the corrected QT interval (QTc; Fridericia correction formula). The ECG was to be performed in the morning. If the QTc interval was prolonged (>450 msec for males or >470 msec for females), the ECG was to be repeated. If still prolonged, the ECG was to be read by a cardiologist at the site for confirmation.
o.	Three consecutive 12-lead ECGs (approximately 2 minutes apart) were performed at baseline (Day 1), 6 hours after the first dose of sunitinib, and on Days 7 and 14 (before dosing) to determine the mean QTc interval (Fridericia correction formula). If the mean QTc interval was prolonged (>450 msec for males or >470 msec for females), the ECG was to be read by a cardiologist at the site for confirmation. Additional ECGs could have been performed as clinically indicated.
p.	Performed at baseline to assess LVEF. Subsequent MUGA or echocardiogram performed only if the subject had signs/symptoms of congestive heart failure.
q.	Treatment started at baseline (Day 1) after completing all predose assessments. Subjects received sunitinib capsules at a starting dose of 37.5 mg daily. Study medication was dispensed at Days 1, 7, and 14; compliance was checked at Days 7 and 14.
r.	Contrast tumor imaging was to be performed within 14 days before treatment. Additional scans were performed whenever disease progression was suspected (eg, symptomatic deterioration).
s.	Subjects were followed for AEs from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. Serious AEs were monitored and reported from the time the subject provided informed consent. Baseline tumor-related signs and symptoms were recorded as AEs during the study if they worsened in severity or increased in frequency.
t.	Study drug compliance was assessed on Days 7 and 14. The study drug medication bottles, including any unused capsules, were returned to the clinic for drug accountability.
u.	Concomitant medications and treatments were recorded from 14 days before the start of study treatment, at study entry, and during the study. Once the subject had withdrawn from the study, concomitant medications and treatments were recorded for 28 days post study treatment, or until all study drug-related toxicities had resolved, whichever was later.

Table 2. Schedule of Activities for Subjects in Main Study

Protocol Activities and Forms to be Completed	Screening ≤14 Days Before Dosing[a]	Treatment With Sunitinib or Imatinib[b]					Post-Treatment		
		Baseline Week 1 Day 1[c] (-1/+0)	Week 3 Day 1 (±3)	Week 5 Day 1 (-1/+0)	Week 9 Day 1 (-1/+0)	Weeks 13, 17, 21, 25, 29, 33, 37, 41, 45, 49 Day 1 (±3)[d]	End of Treatment (Week 53)/ Withdrawal[e] Day 1 (±3)	28 Days Post-Treatment Follow-Up[f] Day 1 (±3)	Survival Follow-Up[g]
Informed consent[h]	X								
Medical/oncology history and demographics[i]	X								
Baseline signs and symptoms[j]		X							
Physical examination[k]	X	(X)[c]		X	X	X	X	X	
Hematology[l,m]	X	(X)	X	X	X	X	X	X	
Blood chemistry[l,n]	X	(X)	X	X	X	X	X	X	
Urinalysis[o]	X			X					
Prothrombin time, partial thromboplastin time, and INR	X	X							
Pregnancy test[p]	X								
Thyroid function test[q]	X								
12-lead ECG[r]	X			X[r]			X		
MUGA or echocardiogram to assess LVEF[s]	X								
Study treatment[t]		X	→X	→X	→X	→X			
Contrast tumor imaging[u]	X			X		X; every 8 weeks	X		
ECOG PS[v], body weight, and vital signs	X	(X)		X	X	X	X	(X)	
Adverse events[w]	X	X	X	X	X	X	X	X	
Study drug compliance[x]				X	X	X	X		
Concomitant medications and treatments[y]	X	X	X	X	X	X	X	X	
PPI of McGill Pain Questionnaire and analgesic use[z]	X	X	X	X	X	X	X		
EQ-5D questionnaire[aa]		X		X	X	X	X		
Post-treatment survival follow-up									X[j]

(X) = if clinically applicable; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQol EQ-5D self-report questionnaire;

Table 2. Schedule of Activities for Subjects in Main Study

INR = International Normalized Ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated angiogram; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PPI = Present Pain Intensity; PS = performance status; QTc = corrected QT (interval); TSH = thyroid-stimulating hormone; WBC = white blood cell.

a. Subjects in the Safety Substudy did not need to perform screening visit procedures again.
b. During treatment, all assessments were performed before dosing with randomized treatment, unless otherwise indicated.
c. Baseline (Week 1, Day 1): hematology, blood chemistry, and physical examination were not required if acceptable screening assessment was performed within 7 days before the start of treatment with randomized treatment. All other activities were required to be performed within –1/+0 day before the start of treatment.
d. Every 4 weeks until final analysis was performed.
e. End of study treatment / withdrawal assessments were obtained if not completed during the previous 2 weeks on study treatment (during the last 6 weeks on study for radiological tumor assessments). These assessments were performed regardless of whether subject completed study treatment or was withdrawn prematurely. Subjects experiencing benefit after completing 1 year on sunitinib were offered continued access to sunitinib on a separate extension protocol.
f. Performed regardless of whether subject completed study treatment or was withdrawn prematurely. Subjects experiencing benefit after completing 1 year on sunitinib study treatment were offered continued access to sunitinib on a separate extension protocol. For those subjects continuing on a separate extension protocol, the 28-day post-treatment follow-up visit was not performed.
g. If the subject was withdrawn from study treatment before completing study treatment, post-treatment survival status was collected by telephone contact every 8 weeks for up to 1 year from the last dose of study medication for each subject.
h. Informed consent was required to be obtained before undergoing any study specific procedures and may have occurred before the 14-day screening period.
i. Included oncologic history, demographics, history of other disease processes (active or resolved), and concomitant illnesses.
j. Subjects were asked about any signs or symptoms experienced within the previous 14 days.
k. Performed during screening, baseline (if applicable), and every 4 weeks beginning at Week 5. Physical examination included examination of major body systems, height (at screening visit only), ECOG PS, body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate). During the 28-day post-treatment follow-up visit, examination was only required for major body systems, body weight, and vital signs.
l. Samples were analyzed using local laboratories.
m. CBC, WBC with differential count, hemoglobin, and platelet count. Subjects in the Safety Substudy did not have screening hematology if the last hematology was performed during the Substudy as scheduled.
n. Total and indirect bilirubin, ALT, AST, alkaline phosphatase, amylase or lipase (baseline only), total protein, albumin, globulin, sodium, potassium, chloride, calcium, magnesium, phosphorus, BUN, creatinine, uric acid, and glucose. Subjects in the Safety Substudy did not have screening chemistry if the last chemistry was performed during the Substudy as scheduled.
o. For urinalysis, in cases of ≥2+ protein, a 24-hour urine to confirm NCI CTCAE was required; dose modification and interruption rules applied by grade for nonhematologic toxicity. Repeat as clinically required.
p. Pregnancy test (serum or urine) for women of reproductive potential; required to be tested within 7 days before the first treatment.
q. Subsequent thyroid tests if clinically indicated (eg, fatigue of CTCAE Grade 3 or greater, abnormal TSH). Recommended follow-up based on institutional standard.
r. Three consecutive 12-lead ECGs performed approximately 2 minutes apart at screening and on Cycle 2, Day 1 to determine the mean QTc interval (Fridericia correction formula). The ECG was to be performed in the morning. If the mean QTc interval was prolonged (>450 msec), the ECG was to be read by a cardiologist at the site for confirmation. Additional ECGs could have been performed as clinically indicated to include 2 weeks following intrapatient dose adjustments.
s. Were performed at screening to assess LVEF. Subsequent MUGA or echocardiogram performed only if subject had signs/symptoms of congestive heart failure.
t. Treatment started at baseline (Week 1, Day 1) after completing all predose assessments. Subjects received sunitinib capsules at a starting dose of 37.5 mg daily or imatinib 800 mg daily. Day 1 dosing occurred at the clinic approximately 24 hours after the last dose of imatinib 400 mg prior to Day 1. For both treatments, dose was adjusted according to individual subject tolerance. Study medication was dispensed and compliance checked beginning at baseline (Week 1, Day 1) and, thereafter, every 4 weeks.

Table 2. Schedule of Activities for Subjects in Main Study

u.	CT or MRI scans required at screening (14 days before start of treatment), Week 5, Day 1, Week 9, Day 1, and thereafter every 8 weeks, to include the chest (screening only), abdomen, and pelvis. The same imaging modality used at baseline was to be continued for each assessment. Subsequent scans were to include areas of known or suspected tumors. Additional scans should have been performed whenever disease progression was suspected (eg, symptomatic deterioration), to confirm a partial or complete response (at least 4 weeks after initial documentation of response), and at the time of withdrawal from the study if >6 weeks since last assessment. Allowable window for Tumor Assessments was ±7 days.
v.	Performed during screening, baseline (if applicable), and every 4 weeks beginning at Week 5. Physical examination included examination of major body systems, height (at screening visit only), ECOG PS, body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate). During the 28-day post-treatment follow-up visit, examination was only required for major body systems, body weight, and vital signs.
w.	Subjects were followed for AEs from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable," whichever was later. Serious AEs were monitored and reported from the time the subject provided informed consent. Baseline tumor-related signs and symptoms were recorded as AEs during the study if they worsened in severity or increased in frequency.
x.	Assessed every 4 weeks beginning on Week 5, Day 1 and at the completion of study treatment. The study drug medication bottles, including any unused capsules, were returned to the clinic for drug accountability.
y.	Concomitant medications and treatments were recorded from 28 days before the start of study treatment, study entry, and during the study. Once a subject had withdrawn from the study, concomitant medications/treatments were recorded 28 days post study treatment, or until all study drug-related toxicities resolved, whichever was later.
z.	Subjects were instructed to record their daily pain intensity and analgesic use 7 days before randomization, then daily throughout therapy. Diaries were collected at baseline, at the start of each visit, and at the completion of therapy.
aa.	This questionnaire was self-administered by the subject in the clinic every 4 weeks and at the end of study treatment/withdrawal.

Number of Subjects (Planned and Analyzed):

Lead-In Safety Substudy (Phase 1): A total of 12 subjects were planned and enrolled in the Substudy. All 12 subjects received a single dose of sunitinib in the Substudy and were analyzed for safety.

Main Study (Phase 3): A total of 200 subjects were planned for enrollment into Main Study. A total of 57 subjects were screened; 31 were randomized to the sunitinib arm, and 26 to the imatinib arm. All 31 subjects randomized to sunitinib received study treatment compared to 25 of 26 subjects randomized to imatinib. All randomized subjects (31 sunitinib and 26 imatinib) were included in the intent-to-treat (ITT) population and were analyzed for efficacy. All treated subjects were included in the as-treated (AT) population and were analyzed for safety.

Of the 69 (12 in the Safety Substudy and 57 in the Main Study) subjects, 22 subjects were enrolled in the UK, 17 in Italy, 16 in the Republic of Korea, 5 in Hong Kong, 3 in the US, 4 in Germany, and 2 in Spain.

Diagnosis and Main Criteria for Inclusion: Both male and female subjects with malignant GIST, who had objectively confirmed disease progression on prior imatinib treatment (400 mg daily), were eligible if they were at least 18 years of age, had adequate organ function, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

Study Treatment:

Lead-In Safety Substudy (Phase 1): Subjects had to take the first dose of sunitinib (37.5 mg) approximately 24 hours following the last dose of imatinib (400 mg) prior to randomization. Treatment was planned to proceed until death, disease progression, or for a period of 1 year. Subsequent to 1 year, subjects receiving clinical benefit from sunitinib treatment were eligible to roll-over to an open-label extension study.

Main Study (Phase 3): Subjects were randomized to receive either open-label sunitinib (37.5 mg daily) or open-label imatinib (800 mg daily). Subjects were treated until disease progression, death, withdrawal from the study, or until the final analysis was performed.

Subjects who received sunitinib were monitored for toxicity and could have their daily dosing interrupted and/or reduced to 25 mg; additionally, the dose could be increased to 50 mg. Subjects who received imatinib could have their daily dosing interrupted and/or reduced to 600 mg. Sunitinib was supplied in hard gelatin capsules containing 12.5 mg, 25 mg, 37.5 mg, or 50 mg equivalents of sunitinib free base. Sunitinib capsules had to be taken orally in the morning with a glass of water and without regard to meals beginning on Day 1 of the study. Imatinib 800 mg had to be taken orally in 2 daily doses after meals.

Efficacy, Pharmacokinetic, Outcomes Research, and Safety Endpoints:

Main Study:

Primary Efficacy Endpoint: The primary endpoint of the Main Study was PFS. PFS was defined as the time from randomization to first progression of disease (PD) on study or death on study for any reason in the absence of documented PD. Analysis of PFS excluded events observed after 28 days post last dose date of study medication. PFS data were censored on the date of the last tumor assessment performed no later than 28 days after the last dose of study medication for subjects who did not have objective tumor progression and who did not die while on study. Subjects who started a new anti-cancer therapy without documented PD prior to start of this therapy were censored on the date of the last tumor assessment prior to the start of the new therapy.

Secondary Endpoints:

- OR was the response recorded from randomization until disease progression. A subject was considered to have achieved an overall OR if the subject had a sustained complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) definitions for at least 4 weeks, confirmed by tumor assessments. Subjects with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) were considered as not having met overall OR criteria.

- TTR was defined as the time from date of randomization to first documentation of OR.

- DR was defined as the time from the first documentation of OR (CR or PR) that was subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. DR data were censored on the day following the date of the last tumor assessment on study for subjects who did not have objective tumor progression and who did not die due to any cause while on study. DR was only calculated for the subgroup of subjects with an OR.

- TTF was defined as the time from date of randomization to: 1) PD; 2) death for any reason; 3) treatment termination due to intolerable toxicity; or 4) withdrawal of consent, whichever occurred first.

- OS (survival time) was defined as the time from date of randomization to date of death. In the absence of confirmation of death, survival time was censored to the last date the subject was known to be alive.

- Pain relief response was defined as a 50% or more reduction in the Present Pain Intensity score of the McGill Pain Questionnaire (MPQ-PPI) and/or analgesic use from baseline for at least 3 consecutive weeks.

- Time-to-Pain Relief (TTPR) was defined as the time from randomization to the first documentation of pain relief response.

- Pain progression was defined as a 50% or more increase in the MPQ-PPI score or analgesic use from the baseline for at least 3 consecutive weeks.

- Time-to-Pain Progression (TTPP) was defined as the time from randomization to the first documentation of pain progression.

- PRO endpoints, derived from the EuroQol EQ-5D Self-Report Questionnaire (EQ-5D), included the EQ-5D descriptive system, EuroQol EQ-5D visual analog scale (EQ-VAS) and EQ-5D Health State (EQ-5D) index.

- Investigator-rated changes in severity of other baseline tumor-related signs and symptoms (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0).

Safety Endpoints:

Lead-In Safety Substudy:

- Treatment-related treatment-emergent AEs (TEAEs) noted during the first week after the initial dose of sunitinib;

- Changes in corrected QT (QTc) interval above 500 msec, changes in QTc interval and predose (trough) levels of sunitinib and SU-012662 were evaluated at 7 and 14 days after the start of sunitinib treatment;

- Elevations in total sunitinib plasma concentrations above those seen at steady state with the approved 50 mg dose (<150 ng/mL).

Substudy and Main Study Combined:

- Safety profile characterized by TEAEs, vital signs and laboratory abnormalities during the study. Assessment of AEs included type, incidence, severity (graded by the NCI CTCAE, Version 3.0), timing, seriousness, and relatedness, and laboratory abnormalities.

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

Safety Evaluations:

Lead-in Safety Substudy (Phase 1): Safety evaluations included assessment of AEs from the first day of treatment to 28 days after the last dose of study drug. Other safety evaluations included changes in QTc interval, elevations in total sunitinib plasma concentrations, and assessment of ECOG PS, clinical laboratory tests (hematology, urinalysis, and serum chemistry performed at screening and Days 1, 7, and 14), ECG (performed at screening and Days 1, 7, and 14), vital signs measurements, thyroid function tests, and left ventricular ejection fraction (LVEF).

Main Study (Phase 3): Safety evaluations included assessment of AEs from the first day of treatment to 28 days after the last dose of study drug. Other safety evaluations included Investigator-rated changes in severity of other baseline tumor-related signs and symptoms (graded by NCI CTCAE, Version 3.0), changes in QTc interval, elevations in total sunitinib plasma concentrations, and assessment of ECOG PS, clinical laboratory tests (hematology, urinalysis, and serum chemistry performed at screening and throughout the study), ECG (performed at screening and throughout the study), physical examinations, vital signs measurements, thyroid function tests, and LVEF.

Statistical Methods: The ITT population included all subjects in the Main Study who were randomized, with study drug assignment designated according to initial randomization, regardless of whether the subject received any study drug or received a different drug from that to which they were randomized. This was the primary population for evaluating all efficacy endpoints (except DR and pain relief response) as well as subject characteristics.

The AT population consisted of all subjects in both the Main Study and the Safety Substudy who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety.

Lead-in Safety Substudy (Phase 1): Safety data were summarized for all subjects receiving at least 1 dose of study medication. Plasma concentrations of sunitinib, SU-012662, and total drug (sunitinib + SU-012662) were summarized using descriptive statistics.

Main Study (Phase 3): All efficacy analyses were performed on the ITT population. All statistical tests were 2-sided with significance level of 0.05.

For time-to-event endpoints (including PFS, DR, TTF, TTPP, and OS), the Kaplan-Meier method was used to obtain the estimates of median event-free time associated with each treatment. The 95% confidence intervals (CIs) of the median event-free time was estimated using standard errors. The stratified Cox proportional hazards model with the previous imatinib treatment status as covariate was used to compute hazard ratio and the corresponding 95% CI.

The planned log-rank tests for the primary and secondary time-to-event endpoints were not performed.

TTR was summarized for each treatment group. The proportion of subjects who achieved an objective tumor response (PR or CR) as well as the proportion who achieved a pain relief response or progression were summarized by treatment arm. The odds radio along with the 95% CI was also be provided.

Analyses of the pain relief response endpoints were based on the pain sample (subjects in the ITT population who recorded pain or analgesic use during the screening period). The proportion of subjects who achieved a pain relief response (pain relief response rate) and the proportion of subjects who had a pain progression (pain progression rate) were computed for each arm and compared by Cochran Mantel-Haenszel tests (stratified for previous imatinib treatment status).

Summary statistics of absolute scores and changes from baseline for EQ-5D Index and EQ-VAS at each assessment time point were calculated.

Safety data were summarized using descriptive statistics.

RESULTS:

Subject Disposition and Demography: Table 3 presents a summary of subject disposition and subjects analyzed in the Safety Substudy.

Table 3. Summary of Subject Disposition and Subjects Analyzed (Phase 1 Safety Substudy)

Number of Subjects	Sunitinib
Screened=12 subjects	
Assigned to study treatment	12
Treated	12
Completed	0
Discontinued	12
Discontinuation related to study drug	1
Adverse event	1
Discontinuation not related to study drug	11
Objective progression or relapse	4
Other	1
Protocol violation	1
Study terminated by sponsor	5
Population groups	
Intent-to-treat (all randomized subjects)[a]	12
As-treated (all treated subjects)	12
Analyzed for safety	
Adverse events	12
Laboratory data	12

Discontinuations occurring outside the lag period were attributed to the last study treatment received.

a. Subjects in the lead-in Safety Substudy were analyzed only for safety; efficacy evaluations were not planned or conducted.

A summary of the subject disposition and subjects analyzed in the Main Study is presented in Table 4.

Table 4. Summary of Subject Disposition and Subjects Analyzed (Phase 3 Main Study)

Number of Subjects	Sunitinib N=31	Imatinib N=26
Screened=57 subjects		
Assigned to study treatment	31	26
Treated	31	25
Completed	0	0
Discontinuations from study	31	26
Subject died	1	1
Discontinuation related to study drug	4	1
Adverse event	4	1
Discontinuation not related to study drug	26	24
Adverse event	1	0
Global deterioration of health status	0	1
Objective progression or relapse	10	13
Other	2	2
Study terminated by sponsor	13	8
Population groups		
Intent-to-treat (all randomized subjects)	31	26
As-treated (all treated subjects)	31	25
Analyzed for safety		
Adverse events	31	25
Laboratory data	30	25

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
N = number of subjects in each group.

Lead-in Safety Substudy (Phase 1): Demographic characteristics are summarized in Table 5. All subjects enrolled in the Phase 1 portion of the study were White. The mean and median age of females (67.4 and 73.0 years, respectively) was higher than the mean and median age of males (54.3 and 57.0 years, respectively). All subjects were considered to have an ECOG PS of 0.

Table 5. Demographic Characteristics - As-Treated Population (Phase 1 Safety Substudy)

Demographic Characteristic	Sunitinib N=12
Gender (n)	
Male	7
Female	5
Age (years)	
<65	7
≥65	5
Median	58.5
Mean	59.8
SD	16.0
Range	32-78
Race (n)	
White	12

N = total number of subjects in the treatment group; n = number of subjects in specified category; SD = standard deviation.

Main Study (Phase 3): Demographic and baseline characteristics are summarized by treatment arm for the ITT population in Table 6.

Table 6. Demographic and Baseline Characteristics - Intent-to-Treat Population (Phase 3 Main Study)

Demographic and Baseline Characteristic	Sunitinib N=31	Imatinib N=26
Gender, n (%)		
Male	20 (64.5%)	15 (57.7%)
Female	11 (35.5%)	11 (42.3%)
Age (years)		
<65	19 (61.3%)	17 (65.4%)
≥65	12 (38.7%)	9 (35.6%)
Mean (SD)	58.1 (10.6)	57.2 (13.4)
Median (range)	58.0 (36-72)	59.5 (21-84)
Race, n (%)		
White	20 (64.5%)	14 (53.8%)
Black	0	2 (7.7%)
Asian	11 (35.5%)	10 (38.5%)
ECOG performance status, n (%)		
0	21 (67.7)	14 (53.8)
1	10 (32.3)	12 (46.2)
Duration of prior imatinib treatment (months)		
N	31	25
<6 months	3 (9.7)	2 (7.7)
≥6 months	28 (90.3)	23 (88.5)
Mean	21.0	26.2
SD	16.3	19.4
Median	15.4	17.7
Range	3.1–80.4	0.4–74.4

ECOG = Eastern Cooperative Oncology Group; N = number of subjects in each treatment group; n = number of subjects in specified category; SD = standard deviation.

Efficacy, Pharmacokinetic, and Outcomes Research Results: This study was stopped prematurely for operational reasons. The planned study objectives on efficacy endpoints (PFS, OR, TTR, DR, TTF, and OS) were changed from comparison between the 2 treatment arms to estimation of the treatment effect.

Primary Efficacy Endpoint: Summary of PFS for the ITT population (Main Study) is presented in Table 7. The median PFS for the sunitinib treated group was 8.6 months (95% CI: 5.7 to 9.0 months) and the imatinib treated group had a median PFS of 6.4 months (95% CI: 4.5 to 15.7 months).

Table 7. Progression-Free Survival - Intent-to-Treat Population (Phase 3 Main Study)

Progression Free Survival Parameter	Sunitinib N=31		Imatinib N=26	
	n	%	n	%
Number of subjects with event	13	41.9	15	57.7
Type of event				
Progressive disease	12	38.7	14	53.8
Death	1	3.2	1	3.8
Number of subjects censored	18	58.1	11	42.3
Reason for censorship				
Still on study	12	38.7	7	26.9
No post-baseline tumor assessment	0	0	1	3.8
Withdrawal due to adverse event	4	12.9	1	3.8
Other	2	6.5	2	7.7
Kaplan-Meier estimates of time to event (months); quartiles (95% CI)[a]				
25%	2.4 (1.0, 8.6)		3.0 (1.8, 6.3)	
50%	8.6 (5.7, 9.0)		6.4 (4.5, 15.7)	
75%	9.0 (8.6, 10.1)		15.7 (6.9, NE)	
Versus imatinib				
Hazard ratio[b]	1.040		-	
95% CI of hazard ratio	0.484-2.235			

CI = confidence interval, N = number of subjects in each treatment group, n = number of subjects with specified criteria; NE = not evaluated.

a. Based on the Brookmeyer and Crowley method.

b. Sunitinib/Imatinib, based on the Cox proportional hazards model stratified by previous imatinib treatment status (<6 months and ≥6 months).

None of the subjects randomized to sunitinib who had a prior duration of imatinib treatment <6 months had a PFS event. One subject randomized to imatinib who had a prior duration of imatinib treatment <6 months had a PFS event, which was due to progressive disease. Thirteen (46.4%) subjects randomized to sunitinib who had a prior duration of imatinib treatment ≥6 months had a PFS event, 12 subjects due to progressive disease and 1 subject due to death. Fourteen subjects (56.0%) randomized to imatinib who had a prior duration of imatinib treatment ≥6 months had a PFS event, 13 subjects due to progressive disease and 1 subject due to death.

Secondary Endpoints Results:

Best Overall Response: Table 8 presents the best overall response for the ITT population (Main Study).

Table 8. Best Overall Response - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Complete response (CR)	0	0
Partial response (PR)	5 (16.1)	2 (7.7)
Stable disease	17 (54.8)	17 (65.4)
Progressive disease	8 (25.8)	6 (23.1)
Unable to evaluate	1 (3.2)	0
Not Assessed	0	1 (3.8)
Objective response rate (CR+PR)	5 (16.1)	2 (7.7)
95% exact CI[a]	(5.5, 33.7)	(0.9, 25.1)
Versus imatinib		
Treatment difference[b]	8.437	
95% CI of difference[b]	(-8.1, 24.9)	
Odds ratio[c]	2.308	
95% CI of odds ratio[c]	(0.4, 13.0)	

The derived assessment was calculated programmatically based on the RECIST criteria.
CI = confidence interval; CR = complete response; N = number of subjects in each group; n = number of subjects with specified criteria; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.
a. Using exact method based on binomial distribution.
b. Calculated based on a normal distribution.
c. Odds ratio is calculated from Mantel-Haenszel logit.

Time-to-Tumor Response: Table 9 presents TTR for the ITT population (Main Study).

Table 9. Time To Tumor Response - Intent To Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Time to tumor response (week)		
Median (95% confidence interval)[a]	4.1 (3.6, 20.1)	40.1 (5.4, 74.7)
Range	(3.6, 20.1)	(5.4, 74.7)

N = number of subjects in each group; n = number of subjects with specified criteria.
a. Based on the Brookmeyer and Crowley method.

Duration of Response: Table 10 present the duration of OR for the ITT population (Main Study).

Table 10. Duration of Objective Response - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Subjects with a response (CR or PR)	5 (16.1)	2 (7.7)
Subject status n (%)		
Subjects with a response and subsequent progression or death due to any cause while on study[a]	0	0
Subjects with a response who have not progressed or died due to any cause while on study[a]	5 (100)	2 (100)
Response duration (weeks)		
Quartiles (95% CI)[b]		
25%	-	-
50%	-	-
75%	-	-
Versus imatinib		
Hazard ratio[c]	-	
95% CI of hazard ratio	-	
Response duration (weeks)		
N	5	2
Mean	17.9	19.8
Median	18.3	19.8
Range	(7.9, 24.1)	(6.7, 32.9)
SD	6.53	18.5

The derived assessment was calculated programmatically based on the RECIST criteria.
CI = confidence interval; CR = complete response; DR = duration of response; N = number of subjects in each group; n = number of subjects with specified criteria; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = standard deviation.

a. On study includes treatment plus 28 day follow-up period.

b. Duration of response (DR) was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of objective tumor progression on study or to death on study due to any cause, whichever occured first. DR only be calculated for the subgroup of subjects with an objective response.

c. The proportional hazards model stratified by previous imatinib treatment status (<6 months and ≥6 months).

Time to Treatment Failure: Table 11 presents the TTF for the ITT population (Main Study).

Table 11. Time to Treatment Failure - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Number with event	16 (51.6)	17 (65.4)
Type of event		
Objective progression	12 (38.7)	14 (53.8)
Treatment termination due to intolerable toxicity	3 (9.7)	1 (3.8)
Death	1 (3.2)	1 (3.8)
Withdrawal of consent	0	0
Missing	0	1 (3.8)
Number censored	15 (48.4)	9 (34.6)
Reason for censorship		
In active follow-up for failure	12 (38.7)	7 (26.9)
Lost to follow-up	0	0
Other	3 (9.7)	2 (7.7)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	2.4 (1.0, 6.4)	3.0 (1.8, 6.3)
50%	8.2 (5.5, 9.0)	6.3 (4.5, 8.2)
75%	9.0 (8.2, 10.1)	11.3 (6.4, -)
Versus imatinib		
Hazard ratio[b]	1.027	
95% CI of hazard ratio	0.505-2.088	

CI = confidence interval; N = number of subjects in each group; n = number of subjects with specified criteria.
a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox proportional hazards model.

Overall Survival: Table 12 presents OS data for the ITT population (Main Study).

Table 12. Overall Survival - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Number of deaths	5 (16.1)	4 (15.4)
Cause of death		
Disease under study	4 (12.9)	3 (11.5)
Study treatment toxicity	0	0
Unknown	0	0
Other	1 (3.2)	1 (3.8)
Number censored	26 (83.9)	22 (84.6)
Reason for censorship		
In follow-up as of data cutoff	25 (80.6)	20 (76.9)
Still alive after 2-year follow-up	0	0
Subject withdrew consent for additional follow-up	1 (3.2)	2 (7.7)
Lost to follow-up	0	0
Number of subjects with last contact date >4 months prior to data cutoff date,and follow-up for survival is <2 years	3 (9.7)	2 (7.7)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	10.7 (5.7, 12.9)	15.1 (10.6, -)
50%	12.9 (10.7, 12.9)	(15.1, -)
75%	12.9 (-, -)	(15.1, -)
Versus imatinib		
Hazard ratio[b]	2.818	
95% CI of hazard ratio	0.640-12.41	

CI = confidence interval; N = number of subjects in each group; n = number of subjects with specified criteria.
a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox Proportional hazards model stratified by previous imatinib treatment status (<6 months and ≥6 months).

Pain Relief Response: Table 13 presents the pain relief response rates for the ITT population.

Table 13. Pain Relief Response - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Subjects with MPQ-PPI and analgesic use data at baseline (n [%])	7 (22.6)	10 (38.5)
Pain relief response rate	2 (6.5)	4 (15.4)
95% exact CI[a]	(0.8, 21.4)	(4.4, 34.9)
Versus imatinib		
Treatment difference[b]	-8.933	
95% CI of difference[b]	(-25.3, 7.4)	
Odds ratio[c]	0.379	
95% CI of odds ratio[c]	(0.1,2.3)	

Pain Relief was defined as a reduction of MPQ-PPI score of at least two points along (or from one point to zero points) with less than 50% increase in analgesic use score or no change in MPQ-PPI score along with a reduction of at least 50% in analgesic use score. The changes were relative to baseline and had to meet the algorithm for 3 consecutive weeks. Subjects with missing baseline scores for either MPQ-PPI or analgesic use were non-evaluable. Also subjects who had baseline scores of 0 for both MPQ-PPI and analgesic use were non-evaluable.
CI = confidence interval; MPQ-PPI = McGill Pain Questionnaire-Present Pain Intensity; N = number of subjects in each group; n = number of subjects with specified criteria.
a. Using exact method based on binomial distribution.
b. Calculated based on a normal distribution.
c. Odds ratio is calculated from Mantel-Haenszel logit.

Time to Pain Relief (TTPR): Table 14 presents TTPR for the ITT population (Main Study).

Table 14. Time-to-Pain Relief - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Time-to-pain relief (day)		
Median (95% confidence interval)	34.0 (11.0, 57.0)	22.0 (8.0, 113.0)
Range	(11.0, 57.0)	(8.0, 113)

Pain relief was defined as a reduction of MPQ-PPI score of at least two points along (or from one point to zero points) with less than 50% increase in analgesic use score or no change in MPQ-PPI score along with a reduction of at least 50% in analgesic use score. The changes were relative to baseline and had to meet the algorithm for 3 consecutive weeks. Subjects with missing baseline scores for either MPQ-PPI or analgesic use were non-evaluable. Also subjects who had baseline scores of zero for both MPQ-PPI and analgesic use were non-evaluable.
MPQ-PPI = McGill Pain Questionnaire-Present Pain Intensity; N = number of subjects in each group; n = number of subjects with specified criteria.

Pain Progression: Table 15 presents pain progression for the ITT population.

Table 15. Pain Progression - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Subjects with MPQ-PPI and analgesic use data at baseline (n [%])	23 (74.2)	21 (80.8)
Pain progression		
Pain progression rate	14 (45.2)	10 (38.5)
95% exact CI[a]	(27.3, 64.0)	(20.2, 59.4)
Versus imatinib		
Treatment difference[b]	6.7	
95% CI of difference[b]	(-18.9, 32.3)	
Odds ratio[c]	1.318	
95% CI of odds ratio[c]	(0.5, 3.8)	

Pain progression was defined as an increase in MPQ-PPI score of at least one point along with less than a 50% reduction in analgesic use score or no change in MPQ-PPI score along with at least a 50% increase in analgesic use score. The changes were relative to baseline and had to meet the algorithm for 3 consecutive weeks.
Subjects with missing baseline scores for either MPQ-PPI or analgesic use were non-evaluable.
CI = confidence interval; MPQ-PPI = McGill Pain Questionnaire-Present Pain Intensity; N = number of subjects in each group; n = number of subjects with specified criteria.
a. Using exact method based on binomial distribution.
b. Calculated based on a normal distribution.
c. Odds ratio is calculated from Mantel-Haenszel logit.

Time to Pain Progression: Table 16 presents TTPP for the ITT population (Main Study).

Table 16. Time-to-Pain Progression - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31 n (%)	Imatinib N=26 n (%)
Number with event	14 (45.2)	10 (38.5)
Number censored	9 (29.0)	11 (42.3)
Kaplan-Meier estimates of time to event (day)		
Quartiles (95% CI)[a]		
25%	8.0 (8.0, 22.0)	8.0 (0.0, 106.0)
50%	22.0 (8.0, 29.0)	99.0 (8.0, 134.0)
75%	29.0 (22.0, 85.0)	134.0 (92.0, 170.0)
Versus imatinib		
Hazard ratio[b]	3.434	
95% CI of hazard ratio	1.057-11.15	

Pain progression was defined as an increase in MPQ-PPI score of at least one point along with less than a 50% reduction in analgesic use score or no change in MPQ-PPI score along with at least a 50% increase in analgesic use score. The changes were relative to baseline and had to meet the algorithm for 3 consecutive weeks.
Subjects with missing baseline scores for either MPQ-PPI or analgesic use were non-evaluable.
CI = confidence interval; MPQ-PPI = McGill Pain Questionnaire-Present Pain Intensity; N = number of subjects in each group; n = number of subjects with specified criteria.
a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox proportional hazards model stratified by previous imatinib treatment status (<6 months and ≥6 months).

EuroQol EQ-5D: Table 17 presents descriptive summary of EQ-5D by visit for the ITT population (Main Study).

Table 17. Descriptive Summary of EuroQol EQ-5D by Visit - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31						Imatinib N=26					
Time Point	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**
EQ-5D Descriptive System: Anxiety/Depression												
BL/Cycle1*	30	1	1.2	0.407	(1, 2)	(1.05, 1.35)	22	1	1.45	0.51	(1, 2)	(1.23, 1.68)
Cycle2	27	1	1.2	0.444	(1, 2.5)	(1.03, 1.38)	23	1	1.3	0.47	(1, 2)	(1.1, 1.51)
Cycle3	21	1	1.19	0.402	(1, 2)	(1.01, 1.37)	20	1	1.4	0.503	(1, 2)	(1.16, 1.64)
Cycle4	23	1	1.22	0.422	(1, 2)	(1.04, 1.4)	18	1	1.33	0.485	(1, 2)	(1.09, 1.57)
Cycle5	16	1	1.19	0.403	(1, 2)	(0.97, 1.4)	17	2	1.59	0.618	(1, 3)	(1.27, 1.91)
Cycle6	16	1	1.13	0.342	(1, 2)	(0.94, 1.31)	12	1.5	1.5	0.522	(1, 2)	(1.17, 1.83)
Cycle7	12	1	1.17	0.389	(1, 2)	(0.92, 1.41)	13	1	1.31	0.48	(1, 2)	(1.02, 1.6)
Cycle8	11	1	1.18	0.405	(1, 2)	(0.91, 1.45)	11	1	1.55	0.688	(1, 3)	(1.08, 2.01)
Cycle9	7	1	1.29	0.488	(1, 2)	(0.83, 1.74)	7	1	1.43	0.535	(1, 2)	(0.93, 1.92)
Cycle10	6	1	1.17	0.408	(1, 2)	(0.74, 1.6)	7	1	1.29	0.488	(1, 2)	(0.83, 1.74)
Cycle11	3	1	1	0	(1, 1)	-	3	1	1.33	0.577	(1, 2)	(-0.1, 2.77)
Cycle12	2	1	1	0	(1, 1)	-	1	1	1	-	(1, 1)	-
EQ-5D Descriptive System: Mobility												
BL/Cycle1*	30	1	1.17	0.379	(1, 2)	(1.03, 1.31)	22	1	1.23	0.429	(1, 2)	(1.04, 1.42)
Cycle2	27	1	1.26	0.447	(1, 2)	(1.08, 1.44)	23	1	1.17	0.388	(1, 2)	(1.01, 1.34)
Cycle3	21	1	1.29	0.463	(1, 2)	(1.08, 1.5)	19	1	1.26	0.452	(1, 2)	(1.05, 1.48)
Cycle4	23	1	1.22	0.422	(1, 2)	(1.04, 1.4)	18	1	1.17	0.383	(1, 2)	(0.98, 1.36)
Cycle5	16	1	1.19	0.403	(1, 2)	(0.97, 1.4)	17	1	1.12	0.332	(1, 2)	(0.95, 1.29)
Cycle6	16	1	1.19	0.403	(1, 2)	(0.97, 1.4)	12	1	1.17	0.389	(1, 2)	(0.92, 1.41)
Cycle7	12	1	1.42	0.515	(1, 2)	(1.09, 1.74)	13	1	1.15	0.376	(1, 2)	(0.93, 1.38)
Cycle8	11	1	1.45	0.522	(1, 2)	(1.1, 1.81)	11	1	1.27	0.467	(1, 2)	(0.96, 1.59)
Cycle9	7	2	1.57	0.535	(1, 2)	(1.08, 2.07)	7	1	1.14	0.378	(1, 2)	(0.79, 1.49)
Cycle10	6	1.5	1.5	0.548	(1, 2)	(0.93, 2.07)	7	1	1.14	0.378	(1, 2)	(0.79, 1.49)
Cycle11	3	1	1.33	0.577	(1, 2)	(-0.1, 2.77)	3	1	1	0	(1, 1)	-
Cycle12	2	1.5	1.5	0.707	(1, 2)	(-4.85, 7.85)	1	1	1	-	(1,1)	-
EQ-5D Descriptive System: Pain/Discomfort												
BL/Cycle1*	30	1	1.23	0.43	(1, 2)	(1.07, 1.39)	22	2	1.55	0.51	(1, 2)	(1.32, 1.77)
Cycle2	27	1	1.46	0.536	(1, 2.5)	(1.25, 1.67)	23	1	1.48	0.511	(1, 2)	(1.26, 1.7)
Cycle3	21	2	1.57	0.507	(1, 2)	(1.34, 1.8)	20	1.5	1.5	0.513	(1, 2)	(1.26, 1.74)
Cycle4	23	1	1.39	0.583	(1, 3)	(1.14, 1.64)	18	1	1.44	0.511	(1, 2)	(1.19, 1.7)
Cycle5	16	1	1.31	0.479	(1, 2)	(1.06, 1.57)	17	1	1.41	0.507	(1, 2)	(1.15, 1.67)
Cycle6	16	1	1.31	0.479	(1, 2)	(1.06, 1.57)	12	1	1.42	0.515	(1, 2)	(1.09, 1.74)
Cycle7	12	1.5	1.5	0.522	(1, 2)	(1.17, 1.83)	13	1	1.46	0.519	(1, 2)	(1.15, 1.78)
Cycle8	11	2	1.55	0.522	(1, 2)	(1.19, 1.9)	11	1	1.55	0.688	(1, 3)	(1.08, 2.01)
Cycle9	7	2	1.57	0.535	(1, 2)	(1.08, 2.07)	7	1	1.36	0.476	(1, 2)	(0.92, 1.8)
Cycle10	6	1.5	1.5	0.548	(1, 2)	(0.93, 2.07)	7	1	1.43	0.535	(1, 2)	(0.93, 1.92)

Table 17. Descriptive Summary of EuroQol EQ-5D by Visit - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31						Imatinib N=26					
Time Point	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**
Cycle11	3	2	1.67	0.577	(1, 2)	(0.23, 3.1)	3	1	1.33	0.577	(1, 2)	(-0.1, 2.77)
Cycle12	2	1	1	0	(1, 1)	-	1	1	1	-	(1, 1)	-
EQ-5D Descriptive System: Self Care												
BL/Cycle1*	30	1	1	0	(1, 1)	-	22	1	1.05	0.213	(1, 2)	(0.95, 1.14)
Cycle2	27	1	1.06	0.212	(1, 2)	(0.97, 1.14)	23	1	1	0	(1, 1)	
Cycle3	21	1	1	0	(1, 1)	-	20	1	1.1	0.308	(1, 2)	(0.96, 1.24)
Cycle4	23	1	1	0	(1, 1)	-	18	1	1	0	(1, 1)	-
Cycle5	16	1	1	0	(1, 1)	-	17	1	1	0	(1, 1)	-
Cycle6	16	1	1	0	(1, 1)	-	12	1	1	0	(1, 1)	-
Cycle7	12	1	1.08	0.289	(1, 2)	(0.9, 1.27)	13	1	1.15	0.555	(1, 3)	(0.82, 1.49)
Cycle8	11	1	1	0	(1, 1)	-	11	1	1.18	0.405	(1, 2)	(0.91, 1.45)
Cycle9	7	1	1	0	(1, 1)	-	7	1	1	0	(1, 1)	-
Cycle10	6	1	1	0	(1, 1)	-	7	1	1	0	(1, 1)	-
Cycle11	3	1	1	0	(1, 1)	-	3	1	1	0	(1, 1)	-
Cycle12	2	1	1	0	(1, 1)	-	1	1	1	-	(1, 1)	-
EQ-5D Descriptive System: Usual Activities												
BL/Cycle1*	30	1	1.23	0.504	(1, 3)	(1.05, 1.42)	22	1	1.32	0.477	(1, 2)	(1.11, 1.53)
Cycle2	27	1	1.3	0.465	(1, 2)	(1.11, 1.48)	23	1	1.3	0.47	(1, 2)	(1.1, 1.51)
Cycle3	21	1	1.19	0.402	(1, 2)	(1.01, 1.37)	18	1	1.39	0.502	(1, 2)	(1.14, 1.64)
Cycle4	23	1	1.28	0.448	(1, 2)	(1.09, 1.48)	18	1	1.22	0.428	(1, 2)	(1.01, 1.43)
Cycle5	16	1	1.19	0.403	(1, 2)	(0.97, 1.4)	17	1	1.18	0.393	(1, 2)	(0.97, 1.38)
Cycle6	16	1	1.13	0.342	(1, 2)	(0.94, 1.31)	12	1	1.33	0.492	(1, 2)	(1.02, 1.65)
Cycle7	12	1	1.33	0.492	(1, 2)	(1.02, 1.65)	12	1	1.25	0.622	(1, 3)	(0.86, 1.64)
Cycle8	11	1	1.36	0.505	(1, 2)	(1.02, 1.7)	11	1	1.45	0.688	(1, 3)	(0.99, 1.92)
Cycle9	6	1.5	1.5	0.548	(1, 2)	(0.93, 2.07)	7	1	1	0	(1, 1)	-
Cycle10	5	2	1.6	0.548	(1, 2)	(0.92, 2.28)	7	1	1	0	(1, 1)	-
Cycle11	3	1	1.33	0.577	(1, 2)	(-0.1, 2.77)	3	1	1	0	(1, 1)	-
Cycle12	2	1	1	0	(1, 1)	-	1	1	1	-	(1, 1)	-
EQ-VAS (Self-Rated Visual Analog Scale)												
BL/Cycle1*	30	82.5	78.13	23.8	(3, 100)	(69.24, 87.02)	22	80	75.41	16.6	(45, 100)	(68.05, 82.77)
Cycle2	27	80	77.19	19.98	(25, 100)	(69.28, 85.09)	22	70.5	73.64	14.61	(41, 100)	(67.16, 80.12)
Cycle3	21	80	78.52	14.24	(56, 100)	(72.04, 85.01)	20	70	72.85	15.24	(50, 100)	(65.72, 79.98)
Cycle4	23	80	80.17	14.28	(45, 99)	(74, 86.35)	18	72.5	76.14	15.78	(50, 100)	(68.29, 83.98)
Cycle5	16	83	84.25	12.3	(60, 100)	(77.7, 90.8)	15	70	68.93	12.82	(40, 81)	(61.83, 76.03)
Cycle6	16	89.5	85.81	13.25	(55, 100)	(78.75, 92.87)	11	69	68.27	15.1	(50, 97)	(58.13, 78.42)
Cycle7	12	80.5	78.25	15.91	(50, 100)	(68.14, 88.36)	12	70	67.08	18.08	(35, 96)	(55.6, 78.57)
Cycle8	11	90	84.73	12.71	(60, 99)	(76.19, 93.26)	10	64.5	63.7	19.23	(35, 90)	(49.94, 77.46)

Table 17. Descriptive Summary of EuroQol EQ-5D by Visit - Intent to Treat (Phase 3 Main Study)

	Sunitinib N=31						Imatinib N=26					
Time Point	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**	**N**	**Median**	**Mean**	**SD**	**Range**	**95% CI**
Cycle9	7	75	82.57	14.3	(70, 100)	(69.34, 95.8)	7	75	74.64	13.26	(52.5, 90)	(62.38, 86.91)
Cycle10	6	76.5	81	12.59	(70, 98)	(67.79, 94.21)	7	78	76.86	8.009	(65, 90)	(69.45, 84.26)
Cycle11	3	75	81	14.93	(70, 98)	(43.9, 118.1)	3	75	75.33	5.508	(70, 81)	(61.65, 89.01)
Cycle12	2	86.5	86.5	16.26	(75, 98)	(-59.62, 232.62)	1	78	78	-	(78, 78)	-
EQ-5D Index (Utility Score)												
BL/Cycle1*	30	1	0.9	0.159	(0.36, 1)	(0.84, 0.95)	22	0.8	0.8	0.117	(0.59, 1)	(0.75, 0.85)
Cycle2	27	0.88	0.84	0.196	(0.21, 1)	(0.76, 0.92)	23	0.81	0.85	0.135	(0.62, 1)	(0.79, 0.91)
Cycle3	21	0.8	0.84	0.13	(0.62, 1)	(0.78, 0.89)	18	0.82	0.82	0.162	(0.52, 1)	(0.74, 0.9)
Cycle4	23	0.85	0.85	0.186	(0.23, 1)	(0.77, 0.93)	18	0.85	0.86	0.143	(0.62, 1)	(0.79, 0.93)
Cycle5	16	1	0.89	0.133	(0.62, 1)	(0.82, 0.96)	17	0.85	0.83	0.217	(0.19, 1)	(0.72, 0.94)
Cycle6	16	1	0.9	0.12	(0.73, 1)	(0.84, 0.96)	12	0.85	0.84	0.157	(0.62, 1)	(0.74, 0.94)
Cycle7	12	0.9	0.84	0.182	(0.52, 1)	(0.72, 0.95)	12	0.82	0.81	0.26	(0.08, 1)	(0.64, 0.97)
Cycle8	11	0.8	0.83	0.168	(0.62, 1)	(0.72, 0.94)	11	0.8	0.68	0.292	(0.05, 1)	(0.48, 0.87)
Cycle9	6	0.74	0.76	0.149	(0.62, 1)	(0.61, 0.92)	7	0.85	0.86	0.105	(0.73, 1)	(0.76, 0.96)
Cycle10	5	0.74	0.78	0.128	(0.69, 1)	(0.62, 0.94)	7	0.85	0.86	0.104	(0.73, 1)	(0.76, 0.96)
Cycle11	3	0.8	0.83	0.157	(0.69, 1)	(0.44, 1.22)	3	0.85	0.88	0.106	(0.8, 1)	(0.62, 1.14)
Cycle12	2	0.93	0.93	0.106	(0.85, 1)	(-0.03, 1.88)	1	1	1	-	(1, 1)	-

*Baseline (BL) was defined as Cycle 1.
N is the number of subjects who completed the scale at the respective cycle.
Raw scores range from 1-3; 1 = not at all, 2 = moderate, 3 = extreme.
Visit windows were applied for the EQ-5D data with the expected Day 1 of each cycle as the mid point.
If a subject had more than one assessment in a given visit window then the average value was used for the purposes of the analysis.
CI = confidence interval; EQ-VAS = EuroQol EQ-5D visual analog scale; N = number of subjects in each group; SD = standard deviation.

Pharmacokinetic Results (Safety Substudy): All treated subjects (n=12) with at least 1 PK sample taken were evaluable for PK analysis. Plasma levels of sunitinib, SU-012662, and total drug (sunitinib + SU-012662) on Day 1 at 6 hours after sunitinib administration (approaching maximum observed concentration [C_{max}]) ranged from 4.1 to 21.8 ng/mL, 0.0 to 2.09 ng/mL, and 4.1 to 23.8 ng/mL, respectively (Table 18).

Trough levels of sunitinib, SU-012662, and total drug (sunitinib + SU-012662) on Day 7 and Day 14 (steady state) ranged from 7.9 to 50.3 ng/mL, 3.2 to 21.0 ng/mL, and 11.3 to 65.5 ng/mL, respectively (Table 18).

Table 18. Summary of Sunitinib, SU-012662, and Total Drug (Sunitinib + SU-012662) Plasma Concentrations (Phase 1 Safety Substudy)

Sample Collection Cycle/Day/Time	N	Sunitinib (ng/mL)		SU-012662 (ng/mL)		Total Drug (ng/mL)	
		Arithmetic Mean (%CV)	Range (Median)	Arithmetic Mean (%CV)	Range (Median)	Arithmetic Mean (%CV)	Range (Median)
Cycle 1/Day 1/6 hours	12	10.61 (42.75)	4.10-21.80 (10.85)	0.84 (108.12)	0.00-2.09 (0.67)	11.45 (44.98)	4.10-23.84 (11.22)
Cycle 1/Day 7/predose	12	31.58 (35.03)	15.60-50.30 (33.00)	7.87 (41.62)	3.21-14.40 (7.12)	39.46 (34.13)	20.41-59.17 (39.33)
Cycle 1/Day 14/predose	12	34.35 (32.79)	7.94-46.40 (39.40)	10.97 (49.23)	3.34-21.00 (10.03)	45.33 (34.64)	11.28-65.50 (47.86)

Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero
CV = coefficient of variation, N = number of subjects.

The study was terminated prematurely for operational reasons.

Safety Results:

Lead-In Safety Substudy and Main Study**:** Table 19 presents an overview of TEAEs (all-causality and treatment-related) during the Substudy (Phase 1).

Table 19. Treatment-Emergent Adverse Events (All Causalities and Treatment-Related) - As-Treated Population (Phase 1 Safety Substudy)

Number of Subjects	Sunitinib N	
	All Causalities	Treatment-Related
Subjects evaluable for AEs	12	12
Number of AEs	64	50
Subjects with AEs	12	12
Subjects with serious AEs[a]	3	2
Subjects with Grade 3 or 4 AEs[b]	5	5
Subjects with Grade 5 AEs[b]	0	0
Subjects discontinued due to AEs	1	1
Subjects with dose reduced due to AEs	2	2
Subjects with temporary discontinuation due to AEs	7	6

AEs and SAEs are not separated out.
Except for the number of AEs, subjects were counted only once in each row.
MedDRA (version 12.1) coding dictionary applied.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (version 3.0); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects meeting specified criteria; NCI = National Cancer Institute; SAE = serious adverse event.
a. Based on Investigator's assessment.
b. Based on NCI CTCAE.

Table 20 presents an overview of TEAEs (all causality and treatment-related) during Main Study (Phase 3).

Table 20. Treatment-Emergent Adverse Events (All Causalities and Treatment-Related) - As-Treated Population (Phase 3 Main Study)

Number of Subjects	Sunitinib n		Imatinib n	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
Subjects evaluable for AEs	31	31	25	25
Number of AEs	307	224	199	112
Subjects with AEs	31	31	24	22
Subjects with serious AEs[a]	8 (25.8%)	2 (6.5%)	5 (20.0%)	4 (16.0%)
Subjects with Grade 3 or 4 AEs[b]	14 (45.2%)	13 (41.9%)	9 (36.0%)	7 (28.0%)
Subjects with Grade 5 AEs[b]	2 (6.5%)	0	1 (4.0%)	0
Subjects discontinued due to AEs	7 (22.6%)	5 (16.1%)	2 (8.0%)	2 (8.0%)
Subjects with dose reduced due to AEs	4 (12.9%)	4 (12.9%)	2 (8.0%)	2 (8.0%)
Subjects with temporary discontinuation due to AEs	16 (51.6%)	14 (45.2%)	10 (40.0%)	7 (28.0%)

AEs and SAEs are not separated out.
Except for the number of AEs, subjects were counted only once in each row.
MedDRA (version 12.1) coding dictionary is applied.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (version 3.0); MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting specified criteria; NCI = National Cancer Institute; SAE = serious adverse event.
a. Based on Investigator's assessment.
b. Based on NCI CTCAE.

Treatment-Emergent Adverse Events (All-Causality): Table 21 presents non-serious TEAEs (all-causality) with an incidence rate of ≥5% in any treatment group reported during the overall study (lead-in Safety Substudy and Main Study).

Table 21. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5 in any Treatment Group

System Organ Class MedDRA (v12.1) Preferred Term	Sunitinib n (%)	Imatinib n (%)
Number (%) of subjects evaluable for adverse events	43[a]	25
Number (%) of subjects with adverse events	43 (100.0)	23 (92.0)
Blood and lymphatic system disorders	15 (34.9)	4 (16.0)
Anaemia	5 (11.6)	2 (8.0)
Neutropenia	9 (20.9)	2 (8.0)
Thrombocytopenia	8 (18.6)	0
Endocrine disorders	3 (7.0)	1 (4.0)
Hypothyroidism	3 (7.0)	1 (4.0)
Eye disorders	1 (2.3)	4 (16.0)
Eyelid oedema	0	2 (8.0)
Lacrimation increased	1 (2.3)	2 (8.0)
Gastrointestinal disorders	32 (74.4)	19 (76.0)
Abdominal discomfort	2 (4.7)	3 (12.0)
Abdominal distension	3 (7.0)	4 (16.0)
Abdominal pain	6 (14.0)	3 (12.0)
Abdominal pain upper	4 (9.3)	3 (12.0)
Constipation	5 (11.6)	4 (16.0)
Diarrhoea	19 (44.2)	8 (32.0)
Dyspepsia	6 (14.0)	1 (4.0)
Flatulence	3 (7.0)	0
Glossodynia	5 (11.6)	0
Nausea	12 (27.9)	9 (36.0)
Oral pain	3 (7.0)	0
Stomatitis	5 (11.6)	1 (4.0)
Vomiting	6 (14.0)	6 (24.0)
General disorders and administration site conditions	28 (65.1)	17 (68.0)
Asthenia	5 (11.6)	2 (8.0)
Face oedema	1 (2.3)	2 (8.0)
Fatigue	13 (30.2)	8 (32.0)
Feeling cold	0	2 (8.0)
Mucosal inflammation	15 (34.9)	0
Oedema	0	5 (20.0)
Oedema peripheral	4 (9.3)	5 (20.0)
Pyrexia	5 (11.6)	2 (8.0)
Infections and infestations	0	2 (8.0)
Upper respiratory tract infection	0	2 (8.0)
Investigations	0	2 (8.0)
Electrocardiogram QT prolonged	0	2 (8.0)
Metabolism and nutrition disorders	7 (16.3)	3 (12.0)
Decreased appetite	7 (16.3)	3 (12.0)
Musculoskeletal and connective tissue disorders	10 (23.3)	2 (8.0)
Arthralgia	3 (7.0)	0
Myalgia	5 (11.6)	0
Pain in extremity	3 (7.0)	2 (8.0)
Nervous system disorders	16 (37.2)	3 (12.0)
Dysgeusia	9 (20.9)	0
Headache	6 (14.0)	2 (8.0)
Lethargy	3 (7.0)	1 (4.0)
Psychiatric disorders	3 (7.0)	2 (8.0)
Insomnia	3 (7.0)	2 (8.0)
Respiratory, thoracic and mediastinal disorders	4 (9.3)	3 (12.0)
Cough	3 (7.0)	2 (8.0)
Oropharyngeal pain	3 (7.0)	0
Pleural effusion	0	3 (12.0)
Skin and subcutaneous tissue disorders	29 (67.4)	9 (36.0)

Table 21. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5 in any Treatment Group

System Organ Class MedDRA (v12.1) Preferred Term	Sunitinib n (%)	Imatinib n (%)
Alopecia	3 (7.0)	1 (4.0)
Blister	4 (9.3)	0
Dry skin	1 (2.3)	3 (12.0)
Hair colour changes	3 (7.0)	0
Palmar-plantar erythrodysaesthesia syndrome	16 (37.2)	0
Periorbital oedema	0	4 (16.0)
Pruritus	1 (2.3)	4 (16.0)
Rash	8 (18.6)	4 (16.0)
Yellow skin	3 (7.0)	0
Vascular disorders	18 (41.9)	1 (4.0)
Flushing	3 (7.0)	1 (4.0)
Hypertension	16 (37.2)	0

The data is for the as-treated population (Phase 1 Safety Substudy and Phase 3 Main Study combined).
Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (version 12.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events.
a. Includes all subjects who received sunitinib in Phase 1 Substudy and Phase 3 Main Study.

Treatment-Related Treatment-Emergent Adverse Events: Table 22 presents treatment-related (sunitinib-related) TEAEs reported in subjects who received sunitinib during the Safety Substudy. The most commonly reported treatment-related AEs were diarrhea (7 [58.3%] subjects), hypertension (5 [41.7%] subjects), and mucosal inflammation (4 [33.3%] subjects). The majority of treatment-related AEs were Grade 1/2 in severity. Grade 3 and Grade 4 treatment-related AEs were experienced by 3 and 2 subjects, respectively.

Table 22. Summary of Treatment Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (All Cycles) - As Treated (Phase 1 Safety Substudy)

System Organ Class Preferred Term	Sunitinib (N=12) n (%)
Any adverse event	12 (100.0)
Blood and lymphatic system disorders	6 (50.0)
Anaemia	2 (16.7)
Neutropenia	3 (25.0)
Thrombocytopenia	3 (25.0)
Endocrine disorders	1 (8.3)
Hypothyroidism	1 (8.3)
Gastrointestinal disorders	10 (83.3)
Abdominal pain upper	1 (8.3)
Diarrhoea	7 (58.3)
Dyspepsia	1 (8.3)
Nausea	2 (16.7)
Stomatitis	1 (8.3)
General disorders and administration site conditions	5 (41.7)
Asthenia	2 (16.7)
Mucosal inflammation	4 (33.3)
Infections and infestations	1 (8.3)
Abscess	1 (8.3)
Investigations	1 (8.3)
Alanine aminotransferase increased	1 (8.3)
Musculoskeletal and connective tissue disorders	2 (16.7)
Arthralgia	1 (8.3)
Muscle haemorrhage	1 (8.3)
Nervous system disorders	3 (25.0)
Dizziness	1 (8.3)
Dysgeusia	3 (25.0)
Renal and urinary disorders	1 (8.3)
Haematuria	1 (8.3)
Respiratory, thoracic and mediastinal disorders	1 (8.3)
Pulmonary embolism	1 (8.3)
Skin and subcutaneous tissue disorders	6 (50.0)
Eczema	2 (16.7)
Palmar-plantar erythrodysaesthesia syndrome	2 (16.7)
Pruritus	1 (8.3)
Rash	1 (8.3)
Skin discolouration	1 (8.3)
Vascular disorders	6 (50.0)
Deep vein thrombosis	1 (8.3)
Hypertension	5 (41.7)

Adverse events reported in this table include both serious and non-serious adverse events, ie, non-serious adverse events and serious adverse events are not separated out.
MedDRA (version 12.1) coding dictionary was applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with adverse events.

Table 23 presents treatment-related TEAEs with an incidence rate of ≥5% in any treatment group reported during the Main Study (Phase 3). The most common treatment-related AEs in subjects treated with sunitinib were palmar-plantar erythrodysesthesia syndrome (n=14), fatigue (n=13), diarrhea (n=12), hypertension (n=11) and mucosal inflammation (n=11).

Table 23. Summary of Treatment Related Treatment-Emergent Adverse Events (With an Incidence Rate of ≥5%) by MedDRA System Organ Class and Preferred Term (All Cycles) - As Treated (Phase 3 Main Study)

System Organ Class Preferred Term	Sunitinib (N=31) n (%)	Imatinib (N=25) n (%)
Blood and lymphatic system disorders	9 (29.0)	5 (20.0)
Anaemia	3 (9.7)	2 (8.0)
Neutropenia	6 (19.4)	2 (8.0)
Thrombocytopenia	5 (16.1)	0
Endocrine disorders	2 (6.5)	0
Hypothyroidism	2 (6.5)	0
Eye disorders	5 (16.1)	6 (24.0)
Conjunctivitis	2 (6.5)	0
Eyelid oedema	0	2 (8.0)
Lacrimation increased	1 (3.2)	2 (8.0)
Gastrointestinal disorders	22 (71.0)	16 (64.0)
Abdominal discomfort	1 (3.2)	2 (8.0)
Abdominal distension	1 (3.2)	2 (8.0)
Abdominal pain upper	2 (6.5)	2 (8.0)
Constipation	2 (6.5)	0
Diarrhoea	12 (38.7)	7 (28.0)
Dry mouth	2 (6.5)	0
Dyspepsia	4 (12.9)	1 (4.0)
Flatulence	2 (6.5)	0
Glossodynia	4 (12.9)	0
Nausea	8 (25.8)	8 (32.0)
Oral pain	3 (9.7)	0
Stomatitis	4 (12.9)	1 (4.0)
Vomiting	6 (19.4)	6 (24.0)
General disorders and administration site conditions	21 (67.7)	16 (64.0)
Asthenia	2 (6.5)	0
Face oedema	1 (3.2)	2 (8.0)
Fatigue	13 (41.9)	7 (28.0)
Mucosal inflammation	11 (35.5)	0
Oedema	0	5 (20.0)
Oedema peripheral	1 (3.2)	4 (16.0)
Injury, poisoning and procedural complications	2 (6.5)	0
Contusion	2 (6.5)	0
Investigations	2 (6.5)	4 (16.0)
Electrocardiogram QT prolonged	0	2 (8.0)
Metabolism and nutrition disorders	8 (25.8)	3 (12.0)
Decreased appetite	7 (22.6)	2 (8.0)
Musculoskeletal and connective tissue disorders	10 (32.3)	1 (4.0)
Arthralgia	2 (6.5)	0
Myalgia	4 (12.9)	0
Pain in extremity	3 (9.7)	0
Nervous system disorders	10 (32.3)	4 (16.0)
Dysgeusia	6 (19.4)	0
Headache	3 (9.7)	2 (8.0)
Respiratory, thoracic and mediastinal disorders	5 (16.1)	2 (8.0)
Cough	2 (6.5)	0
Epistaxis	2 (6.5)	0
Oropharyngeal pain	2 (6.5)	0
Pleural effusion	0	2 (8.0)
Skin and subcutaneous tissue disorders	26 (83.9)	11 (44.0)
Alopecia	3 (9.7)	1 (4.0)
Blister	4 (12.9)	0
Dry skin	1 (3.2)	3 (12.0)
Erythema	2 (6.5)	0

Table 23. Summary of Treatment Related Treatment-Emergent Adverse Events (With an Incidence Rate of ≥5%) by MedDRA System Organ Class and Preferred Term (All Cycles) - As Treated (Phase 3 Main Study)

System Organ Class Preferred Term	Sunitinib (N=31) n (%)	Imatinib (N=25) n (%)
Hair colour changes	3 (9.7)	0
Palmar-plantar erythrodysaesthesia syndrome	14 (45.2)	0
Periorbital oedema	0	3 (12.0)
Pruritus	0	4 (16.0)
Rash	5 (16.1)	4 (16.0)
Yellow skin	3 (9.7)	0
Vascular disorders	13 (41.9)	1 (4.0)
Flushing	2 (6.5)	1 (4.0)
Hypertension	11 (35.5)	0

Adverse events reported in this table include both serious and non-serious adverse events, ie, non-serious adverse events and serious adverse events are not separated out.
MedDRA (version 12.1) coding dictionary was applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with adverse events.

Treatment-Emergent Serious Adverse Events (All-Causality): Treatment-emergent SAEs reported during the overall study (lead-in Safety Substudy and Main Study) are summarized in Table 24.

Table 24. Treatment-Emergent Serious Adverse Events (All Causalities) by System Organ Class and Preferred Term

System Organ Class Preferred Term	Sunitinib (N=43) n (%)	Imatinib (N=25) n (%)
Number of subjects with adverse events	11 (25.6)	5 (20.0)
Cardiac disorders	0	1 (4.0)
Myocardial infarction	0	1 (4.0)
Tachycardia	0	1 (4.0)
Gastrointestinal disorders	6 (14.0)	4 (16.0)
Abdominal distension	0	1 (4.0)
Abdominal pain	0	1 (4.0)
Constipation	0	1 (4.0)
Diarrhoea	2 (4.7)	0
Intestinal obstruction	1 (2.3)	0
Nausea	1 (2.3)	0
Peritonitis	0	1 (4.0)
Rectal haemorrhage	1 (2.3)	0
Upper gastrointestinal haemorrhage	0	1 (4.0)
Vomiting	2 (4.7)	1 (4.0)
General disorders and administration site conditions	2 (4.7)	0
Disease progression	1 (2.3)	0
Pyrexia	1 (2.3)	0
Infections and infestations	2 (4.7)	1 (4.0)
Lower respiratory tract infection	1 (2.3)	0
Lung infection	0	1 (4.0)
Pyelonephritis	1 (2.3)	0
Investigations	0	1 (4.0)
Haemoglobin decreased	0	1 (4.0)
Musculoskeletal and connective tissue disorders	1 (2.3)	0
Muscle haemorrhage	1 (2.3)	0
Nervous system disorders	1 (2.3)	0
Sciatica	1 (2.3)	0
Renal and urinary disorders	0	1 (4.0)
Renal impairment	0	1 (4.0)
Respiratory, thoracic and mediastinal disorders	3 (7.0)	1 (4.0)
Dyspnoea	1 (2.3)	1 (4.0)
Pulmonary embolism	3 (7.0)	0

The data is for the as-treated population (Phase 1 Safety Substudy and Phase 3 Main Study combined).
Subjects were only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (version 12.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in each group; n = number of subjects with adverse events.

Treatment-Emergent Treatment-Related SAEs: Table 25 presents treatment-related SAEs reported during the Safety Substudy.

Table 25. Treatment-Related (Sunitinib-Related) Serious Adverse Events - As-Treated Population (Phase 1 Safety Substudy)

Serious Adverse Event Preferred Term	Sunitinib N=12 n (%)
Muscle hemorrhage	1 (8.3)
Pulmonary embolism	1 (8.3)

Serious adverse events were based on based on Investigator's assessment
MedDRA (version 12.1) coding dictionary was applied.
MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects meeting criteria.

Table 26 presents treatment-related SAEs reported during the Main Study.

Table 26. Treatment-Related Serious Adverse Events - As-Treated Population (Phase 3 Main Study)

Serious Adverse Event[a] Preferred Term[b]	Sunitinib N=31 n (%)	Imatinib (N=25) n (%)
Diarrhea	2 (6.5)[c]	0
Vomiting	2 (6.5)[d]	1 (4.0)[c]
Pyrexia	1 (3.2)[c]	0
Abdominal distension	0	1 (4.0)[c]
Abdominal pain[e]	0	1 (4.0)[c]
Hemoglobin decreased	0	1 (4.0)[c]
Peritonitis	0	1 (4.0)[c]
Renal impairment	0	1 (4.0)[c]
Upper gastrointestinal hemorrhage	0	1 (4.0)[c]

One subject had a serious adverse event of ascites, not included in this table.
MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects, n = number of subjects meeting criteria.
a. Based on Investigator's assessment.
b. MedDRA (version 12.1) coding dictionary was applied.
c. Considered treatment-related.
d. One event of vomiting was considered treatment-related based on Investigator's assessment.
e. Subject also had a serious adverse event of abdominal pain, present before initiation of treatment.

Permanent Discontinuations Due to Adverse Events: Discontinuations due to AEs for the AT population of overall study are presented by treatment arm in Table 27.

Table 27. Discontinuations Due to Adverse Events - As-Treated Population (Phase 1 Safety Substudy/Phase 3 Main Study)

Serial Number (Sex, Age [Years])	System Organ Class[a]	Preferred Term[a]	Treatment Phase	Adverse Event				
				Cycle Start/ Stop	Cycle Start Day/ Stop Day	Study Start Day[b]/ Study Stop Day[b]	Grade/ Outcome	Causality
				Cycle Start/ Stop	Cycle Start Day/ Stop Day	Study Start Day[b]/ Study Stop Day[b]	Grade/ Outcome	Causality
Sunitinib Arm (Lead-In Safety Substudy [Phase 1])								
1 (F, 78)	General disorders and administration site conditions	Asthenia[c]	Active	5/ 7	25/ 2	137/ [>170][d]	3/ still present	Study drug
Sunitinib Arm (Main Study [Phase 3])								
2 (M, 65)	Blood and lymphatic system disorders	Neutropenia[c]	Active	7/ 7	28/ 42	196/ 210	3/ resolved	Study drug
3 (M, 65)	Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome[c]	Active	2/ 2	15/ 29	43/ 57	2/ resolved	Study drug
4 (M, 70)	Renal and urinary disorders	Proteinuria[c]	Active	3/ 3	4/ 15	60/ [>71][d]	3/ still present	Study drug
5 (M, 70)	Nervous system disorders	Dysgeusia[c]	Active	2/ 2	3/ 26	31/ [>54][d]	2/ still present	Study drug
6 (M, 72)	Gastrointestinal disorders	Diarrhea[c,e]	Active	6/ 6	15/ 19	155/ 159	3/ resolved	Study drug
7 (M, 71)	Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism[c,e]	Active	5/ 5	16/ 28	128/ [>140][d]	3/ still present	Disease under study
8 (M, 65)	Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism[c,e]	Active	6/ 6	29/ 29	169/ 169	5/ resolved	Disease under study
Imatinib Arm (Main Study [Phase 3])								
9 (M, 21)	Hepatobiliary disorders	Hepatomegaly[c]	Active	1/ 1	28/ 28	28/ [>28][d]	Grade not reported/ still present	Study drug
10 (F, 84)	Respiratory, thoracic, and mediastinal disorders	Pleural effusion[c]	Active	3/ 4	26/ 20	82/ 104	3/ resolved	Study drug

Subject age was based on screening data. Grade of adverse event was based on NCI CTCAE.
CTCAE = Common Terminology Criteria for Adverse Events (version 3.0), F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, NCI = National Cancer Institute.

a. MedDRA (version 12.1) coding dictionary applied.
b. Day relative to start of study treatment. First day of study treatment = Day 1.
c. Treatment-emergent adverse event.
d. Values in brackets were imputed from incomplete dates and times.
e. Coded by Investigators' assessment as serious adverse event.

Deaths During Lead-In Safety Substudy (Phase 1): No subjects in the lead-in Safety Substudy (Phase 1) died on study (ie, after the first dose of study drug and within 28 days of withdrawal date); 2 subjects died in the follow-up period (ie, >28 days after the withdrawal date). Both of these deaths were related to the disease under study.

Table 28. Summary of Deaths - As-Treated Population (Phase 1 Safety Substudy)

Number of Subjects	Sunitinib N=12 n (%)
Subjects who died on study	0
Subjects who died during follow-up	2 (16.7)
Disease under study	2 (16.7)

On-study deaths were those that occurred after the first dose of study drug and within 28 days of last dose. Follow-up deaths were those that occurred after 28 days of the withdrawal date.
N = number of subjects, n = number of subjects meeting specified criteria.

Deaths During Main Study (Phase 3): Table 29 summarize subject deaths during the Main Study (Phase 3) for the AT population.

Table 29. Summary of Deaths - As-Treated Population (Phase 3 Main Study)

Number of Subject Deaths	Sunitinib N=31		Imatinib N=25	
	n	%	n	%
Number of subject deaths	5	16.1	4	16.0
Subjects who died while on study[a]	2	6.5	1	4.0
Disease under study	2	6.5	0	0
Study treatment related	0	0	0	0
Unknown	0	0	0	0
Other	0	0	1[b]	4.0
Subjects who died during follow-up[c]	3	9.7	3	12.0
Disease under study	2	6.5	3	12.0
Study treatment related	0	0	0	0
Unknown	0	0	0	0
Other	1[d]	3.2	0	0

Subjects could have multiple reasons reported for death.
N = number of subjects, n = number of subjects meeting specified criteria.
a. On-study deaths were those that occurred after the first dose of study drug and within 28 days of last dose.
b. Cause of death most probably due to anteroseptal myocardial infarction.
c. Follow-up deaths were those that occurred after 28 days of withdrawal date.
d. Cause of death due to subject suicide at home.

Electrocardiogram Results:

Lead-In Safety Substudy (Phase 1): There were no Grade 3/4 events related to maximum QTc using using Fridericia's formula (QTcF) interval at baseline or during the study; 2 (16.7%) of 11 subjects had Grade 1 events related to maximum QTcF interval during the study and 2 (16.7%) of 11 subjects had Grade 2 events. None of the QTc interval measurements were greater than 500 msec, plasma drug concentrations achieved in this study did not lead to QTc interval measurements of ≥500 msec.

Main Study (Phase 3): In the sunitinib arm, 2 (6.9%) of 29 subjects had a Grade 1 event related to maximum QTcF during the study; there were no subjects in the sunitinib arm with

Grade 2 or Grade 3/4 events related to maximum QTcF interval during the study. In the imatinib arm, 3 (13.0%) of 23 subjects had a Grade 1 event related to maximum QTcF during the study, 1 (4.3%) subject in the imatinib arm had a Grade 2 event, and 1 (4.3%) subject had a Grade 3/4 event related to maximum QTcF interval during the study.

Other Safety Related Findings: During the Main Study (Phase 3), systolic blood pressure (BP) was slightly higher for subjects in the sunitinib arm than for subjects in the imatinib arm. Beginning with Cycle 1, the mean systolic BP for subjects in the sunitinib arm ranged from 127.0 mm Hg (Cycle 10 [n=4]) to 144.4 mm Hg (Cycle 4 [n=21]); the mean systolic BP for subjects in the imatinib arm ranged from 106.5 mm Hg (Cycle 16 [n=2]) to 126.2 mm Hg (Cycle 1 [n=23]). During the Main Study (Phase 3), diastolic BP was slightly higher for subjects in the sunitinib arm than for subjects in the imatinib arm. Beginning with Cycle 1, the mean diastolic BP for subjects in the sunitinib arm ranged from 80.0 mm Hg (Cycle 10 [n=4]) to 85.1 mm Hg (Cycles 4 [n=21] and 7 [n=11]); the mean diastolic BP for subjects in the imatinib arm ranged from 68.1 mm Hg (Cycle 7 [n=10]) to 80.0 mm Hg (Cycle 21 [n=1]).

During the Main Study (Phase 3) beginning at Week 1 and continuing through Week 73, there was never more than 1 subject per treatment arm (sunitinib or imatinib) with an ECOG PS of 2; all other subjects had an ECOG PS of 0 or 1. By end of treatment in the sunitinib arm, 10 (34.5%) of 29 subjects had an ECOG PS of 0, 17 (58.6%) subjects had an ECOG PS of 1, and 1 (3.5%) subject each had an ECOG PS of 2 and 4. By end of treatment in the imatinib arm, 8 (36.4%) of 22 subjects had an ECOG PS of 0, 13 (59.1%) subjects had an ECOG PS of 1, and 1 (4.6%) subject had an ECOG PS of 2.

CONCLUSIONS:

- Sunitinib 37.5 mg was safely given 24 hours following a 400-mg dose of imatinib in subjects with imatinib-resistant GIST.

- Meaningful comparisons between sunitinib 37.5 mg daily and imatinib 800 mg daily in the treatment of subjects with malignant GIST whose disease had progressed on imatinib 400 mg daily could not be made due to inadequate subject sample size following early study termination for operational reasons.