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

PROTOCOL NO.: A6181111

PROTOCOL TITLE: A Phase III Randomized, Double-Blind Study of Sunitinib (SU011248, Sutent®) Versus Placebo in Patients With Progressive Advanced/Metastatic Well-Differentiated Pancreatic Islet Cell Tumors

Study Centers: A total of 42 centers took part in the study and enrolled subjects; 7 in France, 6 each in the United States and Germany, 5 in Canada, 4 in Spain, 3 each in Belgium, Italy and the United Kingdom, 2 each in Korea and Taiwan and 1 in Australia.

Study Initiation and Final Completion Dates: 07 June 2007 to 15 April 2009. The study was prematurely terminated.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To compare the progression-free survival (PFS) in subjects with pancreatic islet cell tumors treated with sunitinib at a starting dose of 37.5 mg daily (continuous dosing) with those receiving placebo.

Secondary Objectives:

- To compare overall survival (OS) between sunitinib- and placebo-treated subjects.
- To compare objective response (OR) rate between sunitinib- and placebo-treated subjects.
- To compare duration of response (DR) between sunitinib- and placebo-treated subjects in subjects achieving a response.
- To assess time to tumor response (TTR) for sunitinib- and placebo-treated subjects.
- To assess safety and tolerability of sunitinib.
- To assess patient-reported outcomes (PROs).

METHODS

Study Design: This was a multinational, randomized, double-blind, Phase 3 study comparing the efficacy and safety of sunitinib versus placebo in subjects with progressive well-differentiated pancreatic islet cell tumors (pancreatic neuroendocrine tumors [NET]).

Subjects were randomized in a 1:1 fashion to receive either sunitinib 37.5 mg once daily on a continuous daily dosing schedule or matching placebo. Subjects on both treatment arms received best supportive care in addition to the study treatment. The primary endpoint of the study was PFS. Subjects were to receive study treatment until documentation of objective disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, unacceptable toxicity, or death. At the time of disease progression, subjects randomized to placebo were unblinded and offered access to sunitinib treatment in one of two separate, open-label extension studies.

This study was designed to detect a 50% improvement in median PFS with a target enrollment of 340 subjects. An interim analysis was planned when 130 events had occurred and the final analysis was to be conducted when 260 events had occurred. The conduct of the study was overseen by an independent Data Monitoring Committee (DMC).

After 73 PFS events had occurred, the independent DMC determined that the study had met its primary endpoint early, demonstrating an advantage for sunitinib, and recommended that the study be stopped and that study treatment assignments be unblinded. The sponsor offered subsequent access to open-label sunitinib for all Study A6181111 subjects on one of two extension studies.

The Schedule of Events for Study A6181111 is presented in Table 1.

Table 1. Schedule of Events

Protocol Activities and Forms to be Completed	Screening	Administration of Sunitinib or Placebo[a]				Post-Treatment		
	≤21 Days Prior to Dosing	Month 1 (Week 1, Week 3)		Subsequent Months (Week 5, 9, 13, 17, etc.)		End of Treatment or Withdrawal[d]	28 Days Post-Treatment[e]	Survival Follow-Up
		Day 1[b] –1/+0	Day 15 –3/+3	Day 1 –3/+3	Day 15[c] –3/+3			
Informed consent[f]	X							
Medical/oncology history[g] and demographics	X							
Baseline signs and symptoms		X						
Physical examination, ECOG PS, body weight, height, and vital signs[h]	X	{X}		X		X	{X}	
Urine protein dipstick[i]	X			Xi				
Hematology, blood chemistry, thyroid function testing[j]	X	{X}	X	X	{X}	X	{X}	
Pregnancy test[k]	X							
12-lead ECG[l]	X			X (Week 5)		X		
Ki-67 assessment[m]	(X)							
MUGA or echocardiogram[n]	X							
Study randomization[o]	X							
Study treatment[p]		X		X				
Tumor imaging[q]	X			X Every 8 weeks after Week 9		X		
EORTC QLQ-C30[r]		X		X		X		
Adverse events[s]	X	X	X	X	X	X	X	
Study drug compliance[t]			X	X		X		
Concomitant medications and treatments[u]	X	X	X	X	X	X	X	
Poststudy survival status[v]								X

{ } = if applicable; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ = European Organization for Research and Treatment of Cancer quality of life questionnaire; MUGA = multigated acquisition; QTc = corrected QT; T3 = triiodothyronine; T4 = Thyroxine.

a. During treatment: All assessments performed prior to dosing with sunitinib or placebo unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. The term "month" was taken to mean a 28-day period.

b. Month 1 Day 1: Hematology, blood chemistry, and physical examination not required if acceptable screening assessment performed within 7 days prior to the start of treatment with sunitinib or placebo.

c. Only if dose escalated. Day 15 beyond Month 2: Dose could have been escalated at any time following 8 weeks. If dose escalated from 37.5 to 50 mg daily, clinic visit was required mid-month for 2 months.

d. Assessments done if not completed during the previous 2 weeks on study (during the last 6 weeks on study for radiological tumor assessments).

e. Collected by telephone contact every 8 weeks until final overall survival update or 5 years after all subjects enrolled, whichever was earlier. For subjects who entered an extension study, follow-up for overall survival was conducted as part of the extension study.

f. Obtained prior to undergoing any study-specific procedure and could have occurred prior to the 21-day screening period.

Table 1. Schedule of Events

g. Included information on prior treatment regimens, including dosing and duration of administration, plus description of best response observed and treatment failure.
h. Examination of major body systems, height (at Screening visit only), ECOG Performance Status, body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate).
i. Dipstick analysis, protein at Screening and Week 5. In cases of ≥2+ protein, a 24-hour urinalysis to confirm National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade was required and dose interruption and modification rules by grade for non-hematologic toxicity were to be applied. Repeated as clinically indicated.
j. Prothrombin time and partial thromboplastin time only required once at Screening. Thyroid function testing consisted of thyroid-stimulating hormone at screening, subsequent thyroid function tests only as clinically indicated. Recommended follow-up based on institutional standard free T4, T3, total, thyroglobulin could have been considered.
k. Pregnancy test must have been within 7 days of starting study treatment.
l. Three consecutive 12-lead ECGs approximately 2 minutes apart at Screening and on Cycle 2 Day 1 to determine the mean QTc interval. If the mean QTc interval was prolonged (>500 msec), the ECGs were to have been overread by a cardiologist at the site for confirmation. Additional ECGs could have been performed as clinically indicated.
m. Assessment based on previous tumor biopsy results or previous surgical resections provided.
n. Subsequent post-screening evaluation of left ventricular ejection fraction required only if subject exhibited clinical signs/symptoms of congestive heart failure.
o. Subject number obtained from the sponsor.
p. Treatment started on Day 1 after completing all predose assessments. Subjects received either sunitinib capsules at a starting dose of 37.5 mg or placebo, according to randomization. The dose could have been adjusted according to individual subject tolerance.
q. Computed tomography or magnetic resonance imaging scans at screening included chest, abdomen, pelvis and brain as well as a bone scan. Subsequent scans may have included only areas of known or suspected tumors. Additional scans were to 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). Subsequent brain scans (after screening) were only performed if symptoms suggested brain metastases, and bone scans (after screening) only needed be performed if the subject had bone metastases at screening or if subsequent bone metastases were suspected/documented. Tumor imaging was performed at screening, Week 5, Week 9, and then every 8 weeks thereafter.
r. The questionnaire was self-administered in the clinic. The questionnaire was to be completed before any interventions (eg, laboratory assessments or study drug administration) every month post-baseline assessment.
s. Subjects were followed for adverse events 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 were resolved or were determined to be “chronic” or “stable,” whichever was later. Serious adverse events were monitored and reported from the time that the subject provided informed consent. For adverse events occurring near the end of the study in subjects who were entering an extension study, the adverse events were followed as part of the extension study.
t. The study drug medication bottle(s) including any unused capsules were to be returned to the clinic for drug accountability.
u. Recorded from 28 days prior to the start of study treatment until 28 days after last treatment.
v. For those subjects who did not enter an extension study. For subjects who entered an extension study, all follow-up was to be performed as part of the extension study.

Number of Subjects (Planned and Analyzed): A total of 340 subjects were planned to be enrolled. A total of 171 subjects were actually enrolled and analyzed (60 in France, 17 in Canada, 16 in Germany, 14 in the United States, 13 in Belgium, 13 in Korea, 12 in the United Kingdom, 10 in Spain, 8 in Taiwan, 4 in Australia, and 4 in Italy. A total of 171 subjects were randomized to study treatment (86 subjects in sunitinib arm and 85 subjects in placebo arm), of whom 165 subjects were treated and analyzed. A total of 6 subjects were randomized but not treated (3 subjects randomized to sunitinib and 3 subjects randomized to placebo).

Diagnosis and Main Criteria for Inclusion: Subjects with well-differentiated advanced/metastatic pancreatic islet cell tumor, with disease progression within the past year. Subjects were excluded if they had current treatment with any chemotherapy, chemoembolization therapy, immunotherapy, or investigational anticancer agent other than somatostatin analogs or prior treatment with any tyrosine kinase inhibitors or anti-vascular endothelial growth factor angiogenic inhibitors.

Study Treatment: Subjects were randomized in a 1:1 fashion to receive either oral sunitinib 37.5 mg once daily on a continuous daily dosing schedule or matching placebo, beginning on Day 1 of the study. Subjects were monitored for toxicity, and the sunitinib dose could have been adjusted according to individual subject tolerance. Sunitinib and matching placebo were provided as hard gelatin capsules.

Efficacy and Outcomes Research Endpoints:

Primary Endpoint:

- Progression Free Survival: The primary endpoint was PFS, which was defined as the time from date of randomization to first progression of disease (PD) or death for any reason in the absence of documented PD. PFS data were censored on the date of the last tumor assessment on study for subjects who did not have objective tumor progression and who did not die while on study. Subjects lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with a duration of 1 day. Additionally, subjects who started a new anti-cancer therapy prior to documented PD were censored at the date of the last tumor assessment prior to the start of the new therapy.

Secondary Endpoints:

- Overall survival (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 last date the subject was known to be alive. .

- Objective response (OR) rate: The OR was the overall objective response recorded from randomization until disease progression. A subject was considered to have achieved an OR if the subject had a sustained complete response (CR) or partial response (PR) according to RECIST definitions for at least 4 weeks, confirmed by repeat tumor assessments. Otherwise, the subject was considered as not meeting OR criteria.

Additionally, subjects with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) were considered as not meeting OR criteria.

- Duration of response (DR): 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 or to death due to any cause, whichever occurred first. DR data were censored on 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.

- Time-to-tumor-response (TTR): TTR was defined as the time from date of randomization to first documentation of objective tumor response that was subsequently confirmed.

- Patient reported outcomes (PROs): PROs were defined as health-related quality of life using the self-administered European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire -C30 (EORTC QLQ-C30). Subjects completed the questionnaire at the clinic prior to administration of study medications or other clinical activities on Day 1 and every 4 weeks thereafter as well as at end of treatment/withdrawal.

Safety Evaluations: Safety profile was characterized by Treatment-Emergent Adverse Events (TEAEs), which were defined as all AEs (serious and non-serious) reported from the first day of study treatment through 28 days post last dose of study treatment, vital signs and laboratory abnormalities. Assessment of AEs included type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse events [CTCAE], Version 3.0), timing, seriousness, and relatedness, and laboratory abnormalities. Baseline tumor-related signs and symptoms were recorded as AEs during the trial if they worsened in severity or increased in frequency.

Statistical Methods: Analysis Sets:

Intent-to-Treat Population (ITT): All subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects 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 as well as subject characteristics.

As-Treated Population: All subjects who received at least 1 capsule 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.

Patient Reported Outcome (PRO) Population: All subjects from the ITT population who completed at least 1 EORTC QLQ-C30 assessment while on treatment.

Efficacy Analysis: The primary analysis of PFS was performed in the ITT population based on the Investigator's assessment of tumor response. An unstratified log-rank test (2-sided) was used to compare PFS time between the 2 treatment arms with nominal significance level 0.049 (2-sided) for the primary endpoint analysis (after the adjustment for 1 interim analysis). The Kaplan-Meier method was used to obtain the estimates of median event-free time associated with each treatment arm with the corresponding two-sided confidence interval (CI). The hazard ratio and its 95% CI were estimated.

The number and percentage of subjects achieving OR (CR or PR) was summarized along with the corresponding exact 2-sided 95% CI calculated using a method based on the F distribution. Fisher's exact test was used to compare ORR between the 2 treatment arms. Best OR was summarized by treatment arm. The best response of stable disease (SD) was assigned if SD criteria were met at least once after randomization and persisted for at least 6 weeks. DR (in responders only), TTR, and OS were to be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event times and 95% CI for the medians were provided.

PRO Analysis: EORTC QLQ-C30 data were described using summary statistics and analyzed using repeated measures mixed-effects models.

Safety Analysis: Descriptive statistics were presented, where appropriate, for the safety parameters.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition and subjects analyzed is provided in Table 2.

A total of 171 subjects were randomized to study treatment (sunitinib or placebo), of whom 165 subjects were treated. A total of 6 subjects were randomized but not treated. With the exception of 1 subject, all had been in the screening phase for enrollment when the decision to terminate Study A6181111 was made.

Table 2. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Sunitinib	Placebo
Assigned to study treatment	86	85
Treated	83	82
Randomized, not treated in Study A6181111	3	3
Discontinued	83	82
Objective progression or relapse	19 (22.1)	47 (55.3)
Study terminated by sponsor	41 (47.7)	16 (18.8)
Adverse event	15 (17.4)	7 (8.2)
Global deterioration of health status	1 (1.2)	5 (5.9)
Subject died	1 (1.2)	3 (3.5)
Protocol violation	2 (2.3)	1 (1.2)
Subject refused continued treatment for reason other than adverse event	2 (2.3)	1 (1.2)
Other	1 (1.2)	1 (1.2)
Lost to follow-up	0	1 (1.2)
Withdrawn due to pregnancy	1 (1.2)	0
Analyzed for efficacy (ITT population)[a]		
Best overall response	86 (100.0)	85 (100.0)
DR/PFS/OS[b]	86 (100.0)	85 (100.0)
Analyzed for safety (As Treated population)		
Adverse events	83 (96.5)	82 (96.5)
Laboratory data	82 (95.3)	80 (94.1)

DR = duration of response; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.
a. Time to tumor response was also analyzed in this population.
b. DR analyzed only for subset of subjects who were responders (8 subjects on the sunitinib arm).

Demographic and baseline characteristics are summarized by treatment arm for the ITT population in Table 3.

Table 3. Summary of Demographic and Baseline Characteristics – ITT Population

	Sunitinib (N=86)	Placebo (N=85)
Sex (number of subjects)		
Male	42	40
Female	44	45
Age (years)		
Mean (standard deviation)	55.4 (13.6)	55.9 (12.7)
Median (minimum-maximum)	56.0 (25-84)	57.0 (26-78)
Race (number of subjects)		
White	48 (55.8)	53 (62.4)
Asian	13 (15.1)	10 (11.8)
Other	25 (29.1)	21 (24.7)
Unspecified	0	1 (1.2)
Weight (kg)		
Mean (standard deviation)	68.0 (14.9)	66.7 (15.1)
Median (minimum-maximum)	67.4 (40.0-105.9)	65.4 (37.0-127.4)
n	86	84
Height (cm)		
Mean (standard deviation)	168.3 (10.0)	167.5 (9.7)
Minimum-maximum	147.0-200.0	147.5-192.0
n	85	83
ECOG Performance Status (number of subjects)		
0	53 (61.6)	41 (48.2)
1	33 (38.4)	43 (50.6)
2	0	1 (1.2)

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; N = number of subjects randomized; n = number of subjects with data.

Efficacy and Other Outcome Results: A clinically significant improvement in PFS, the primary endpoint of the study, was observed in favor of sunitinib in subjects with progressive, well-differentiated pancreatic NET. A median PFS of 11.4 months was observed on the sunitinib arm, and a median PFS of 5.5 months was observed on the placebo arm, with a hazard ratio of 0.418 and p-value of 0.0001 based on a total of 81 events.

OS and ORR were secondary efficacy endpoints. The hazard ratio for OS based on 30 events was 0.409 (95% CI: 0.187, 0.894; p=0.0204) favoring sunitinib over placebo. The ORR as determined by Investigator assessment was statistically significantly higher on the sunitinib arm than on the placebo arm (9.3% vs. 0%, respectively; 95% CI: 3.2, 15.4; p=0.0066). Median TTR, in terms of the Kaplan-Meier estimate of time to event for the ITT population, could not be estimated due to the number of responders; however, among those subjects with an objective tumor response (8 subjects on the sunitinib arm), the median TTR was 3.1 months (range 0.8-11.1 months). Median DR among subjects who had a response could not be estimated because 7 of the 8 responding subjects had ongoing responses at the time of data cutoff. The results of these primary and secondary efficacy endpoints are summarized in Table 4.

Table 4. Overview of Efficacy Endpoints-ITT Population

Endpoint	Sunitinib (N=86)	Placebo (N=85)	Hazard Ratio (95% CI)	p-value
Primary Endpoint				
Progression-free survival (months)				
Median (95% CI)	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.418 (0.263, 0.662)	0.0001
Secondary Endpoints				
Overall survival (months)				
Median (95% CI)	20.6 (20.6, NR)	NR (15.5, NR)	0.409 (0.187, 0.894)	0.0204
Objective response (ORR)				
Number (%) of subjects[a]	8 (9.3)	0		0.0066
Complete response	2 (2.3)	0		
Partial response	6 (7.0)	0		
Stable disease (stable/no response)	54 (62.8)	51 (60.0)		
Progressive disease	12 (14.0)	23 (27.1)		
Indeterminate	12 (14.0)	11 (12.9)		
Time to tumor response (months)[b]				
Median (range)	3.1 (0.8-11.1)	NA		
Median Duration of response	NR	NA		

Results are from the ITT population, with tumor-related endpoints based on Investigator assessments according to RECIST (excluding the OS analysis).
CI = confidence interval; CR = complete response; ITT = intent-to-treat; N = number of subjects randomized; NA = not applicable; NR = not reached; OR = objective response; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.
a. Results for OR (ORR) are given in number (%) of subjects having a confirmed CR or PR.
b. Responders only (8 subjects on the sunitinib arm).

EORTC QLQ-C30 Results: Absolute scores for all 15 subscales of the EORTC QLQ-C30 are summarized in Table 5.

Differences in the 15 scales of the EORTC QLQ-C30 between the 2 treatment arms were calculated using the repeated measures mixed effects model and are summarized in Table 6.

The scores and the between-treatment arm differences are presented for up to Cycle 10. Later time points are not presented due to the relatively small number of remaining subjects in each treatment arm.

Table 5. Summary of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Scales - Absolute Scale Scores by Cycle - PRO Analysis Set

Subscale	Sunitinib (N=73)		Placebo (N=71)	
	n	Mean (SD)	n	Mean (SD)
Global quality of life				
Cycle 1	66	67.0 (20.3)	66	64.0 (22.7)
Cycle 2	68	62.1 (19.9)	66	62.6 (23.6)
Cycle 3	60	62.6 (20.7)	56	63.5 (25.1)
Cycle 4	55	62.0 (21.8)	43	61.6 (23.3)
Cycle 5	48	63.5 (21.9)	40	61.7 (25.4)
Cycle 6	42	66.9 (22.0)	31	56.7 (29.8)
Cycle 7	37	66.2 (23.0)	28	64.6 (23.4)
Cycle 8	33	65.9 (23.6)	22	62.1 (23.2)
Cycle 9	33	67.2 (19.1)	18	64.4 (22.1)
Cycle 10	29	71.0 (20.1)	14	59.5 (24.0)
Cognitive functioning				
Cycle 1	67	87.1 (16.6)	66	87.1 (18.2)
Cycle 2	69	82.9 (20.0)	66	78.5 (24.4)
Cycle 3	60	80.1 (19.9)	56	80.8 (22.7)
Cycle 4	55	79.7 (24.2)	43	82.6 (18.5)
Cycle 5	48	82.3 (20.2)	40	82.9 (21.8)
Cycle 6	42	82.1 (22.5)	31	82.3 (20.6)
Cycle 7	38	84.6 (21.0)	28	88.1 (15.6)
Cycle 8	34	84.3 (18.3)	22	79.5 (23.0)
Cycle 9	33	80.3 (21.8)	18	83.3 (18.1)
Cycle 10	29	80.5 (24.0)	14	85.7 (19.5)
Emotional functioning				
Cycle 1	67	75.2 (23.0)	66	73.7 (26.2)
Cycle 2	69	76.2 (22.1)	66	73.1 (27.1)
Cycle 3	60	75.3 (20.2)	56	70.8 (25.8)
Cycle 4	55	72.2 (23.2)	43	76.9 (22.3)
Cycle 5	48	72.6 (25.2)	40	75.8 (23.9)
Cycle 6	42	77.8 (23.8)	31	72.8 (28.9)
Cycle 7	38	75.3 (28.6)	28	80.8 (19.8)
Cycle 8	34	74.0 (30.9)	22	76.7 (21.6)
Cycle 9	33	75.4 (23.4)	18	75.8 (30.0)
Cycle 10	29	76.4 (23.4)	14	76.2 (20.4)
Physical functioning				
Cycle 1	67	83.1 (20.5)	66	83.1 (20.6)
Cycle 2	69	77.7 (20.5)	67	77.1 (25.9)
Cycle 3	60	78.2 (21.6)	56	75.5 (28.5)
Cycle 4	55	77.5 (21.3)	43	78.4 (24.5)
Cycle 5	48	78.3 (20.2)	40	80.7 (21.9)
Cycle 6	42	80.9 (16.3)	30	81.1 (22.3)
Cycle 7	38	80.3 (18.8)	28	78.9 (25.4)
Cycle 8	34	79.4 (20.7)	22	73.5 (28.1)
Cycle 9	33	78.8 (17.0)	18	79.6 (24.8)
Cycle 10	29	81.4 (18.9)	14	78.6 (23.3)
Role functioning				
Cycle 1	67	84.3 (23.4)	66	77.5 (27.7)
Cycle 2	69	71.6 (28.9)	67	68.9 (30.6)
Cycle 3	60	71.0 (26.7)	56	70.5 (31.0)
Cycle 4	55	72.1 (28.9)	43	73.3 (29.6)
Cycle 5	48	71.5 (27.7)	41	75.0 (31.4)
Cycle 6	42	76.6 (26.6)	31	66.1 (32.6)
Cycle 7	38	75.7 (28.8)	28	72.3 (29.7)
Cycle 8	34	73.0 (29.6)	22	66.7 (30.9)

Table 5. Summary of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Scales - Absolute Scale Scores by Cycle - PRO Analysis Set

Subscale	Sunitinib (N=73)		Placebo (N=71)	
	n	Mean (SD)	n	Mean (SD)
Cycle 9	33	72.2 (24.2)	18	67.6 (31.6)
Cycle 10	29	79.9 (22.4)	14	70.2 (28.6)
Social functioning				
Cycle 1	67	79.4 (27.2)	66	77.0 (31.5)
Cycle 2	69	77.8 (22.1)	66	75.0 (31.0)
Cycle 3	60	77.1 (23.1)	56	77.2 (28.8)
Cycle 4	55	71.2 (28.4)	43	79.8 (26.1)
Cycle 5	48	74.3 (23.8)	40	77.3 (30.2)
Cycle 6	42	79.0 (26.3)	31	74.7 (31.0)
Cycle 7	38	76.3 (29.2)	28	83.9 (25.5)
Cycle 8	34	72.5 (30.4)	22	74.2 (31.6)
Cycle 9	33	76.3 (21.7)	18	74.1 (33.4)
Cycle 10	29	75.9 (25.8)	14	81.0 (24.3)
Appetite loss				
Cycle 1	67	16.9 (25.5)	66	18.7 (27.5)
Cycle 2	69	25.1 (33.0)	67	20.4 (31.8)
Cycle 3	60	25.0 (34.5)	56	23.8 (32.9)
Cycle 4	55	33.3 (34.5)	43	22.5 (27.9)
Cycle 5	48	26.4 (33.7)	41	24.0 (30.7)
Cycle 6	42	20.6 (30.3)	31	23.7 (30.1)
Cycle 7	38	24.6 (29.7)	28	19.0 (29.3)
Cycle 8	34	24.5 (31.0)	21	30.2 (33.2)
Cycle 9	33	23.2 (27.0)	18	22.2 (32.3)
Cycle 10	29	18.4 (29.0)	14	21.4 (33.6)
Constipation				
Cycle 1	67	14.9 (24.8)	65	14.9 (23.6)
Cycle 2	69	8.2 (16.6)	66	13.6 (23.4)
Cycle 3	59	9.0 (20.4)	56	18.5 (28.4)
Cycle 4	55	9.1 (17.5)	43	14.0 (24.4)
Cycle 5	48	7.6 (17.2)	41	15.9 (24.7)
Cycle 6	42	11.1 (15.9)	31	14.0 (26.9)
Cycle 7	37	9.9 (19.0)	28	10.1 (23.7)
Cycle 8	34	11.8 (18.1)	22	18.2 (32.1)
Cycle 9	32	10.4 (15.7)	18	18.5 (32.8)
Cycle 10	29	13.8 (18.9)	14	16.7 (31.4)
Diarrhea				
Cycle 1	67	20.4 (29.6)	66	19.2 (28.1)
Cycle 2	69	37.7 (35.2)	66	18.2 (27.5)
Cycle 3	60	34.2 (33.7)	56	16.7 (26.2)
Cycle 4	55	38.8 (32.6)	43	18.6 (27.5)
Cycle 5	47	42.6 (36.6)	40	15.0 (25.0)
Cycle 6	42	38.9 (32.9)	31	18.3 (28.3)
Cycle 7	38	41.7 (30.0)	28	16.7 (29.4)
Cycle 8	33	43.4 (31.7)	22	15.9 (26.5)
Cycle 9	33	40.4 (29.8)	18	14.8 (20.5)
Cycle 10	29	40.2 (32.6)	14	9.5 (15.6)
Dyspnea				
Cycle 1	67	15.9 (21.2)	66	19.7 (29.2)
Cycle 2	69	23.2 (26.4)	66	22.7 (29.3)
Cycle 3	60	20.6 (24.6)	56	20.8 (30.2)
Cycle 4	55	25.5 (26.4)	43	22.5 (27.9)
Cycle 5	48	20.8 (27.2)	41	16.3 (22.5)
Cycle 6	42	19.0 (23.4)	30	15.6 (31.2)

Table 5. Summary of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Scales - Absolute Scale Scores by Cycle - PRO Analysis Set

Subscale	Sunitinib (N=73)		Placebo (N=71)	
	n	Mean (SD)	n	Mean (SD)
Cycle 7	38	19.3 (24.1)	28	19.6 (26.1)
Cycle 8	34	22.5 (28.1)	22	21.2 (30.1)
Cycle 9	32	25.0 (25.4)	18	18.5 (28.5)
Cycle 10	29	18.4 (26.1)	14	16.7 (25.3)
Fatigue				
Cycle 1	67	29.4 (23.7)	66	34.5 (26.4)
Cycle 2	69	44.3 (24.2)	67	40.1 (30.1)
Cycle 3	60	41.2 (23.6)	56	42.3 (32.6)
Cycle 4	55	41.0 (26.0)	43	37.0 (29.5)
Cycle 5	48	34.7 (23.4)	41	36.3 (31.8)
Cycle 6	42	34.9 (25.9)	31	42.3 (33.1)
Cycle 7	38	36.5 (24.9)	28	34.9 (27.2)
Cycle 8	34	39.9 (28.4)	22	43.2 (33.0)
Cycle 9	33	37.4 (22.5)	18	37.7 (27.8)
Cycle 10	29	33.7 (23.7)	14	43.7 (30.3)
Financial difficulties				
Cycle 1	67	19.9 (32.3)	66	15.7 (27.6)
Cycle 2	68	14.2 (26.0)	65	14.4 (26.3)
Cycle 3	59	15.8 (25.8)	56	16.7 (28.4)
Cycle 4	55	18.2 (27.8)	43	12.4 (27.2)
Cycle 5	48	18.1 (28.3)	40	13.3 (24.8)
Cycle 6	42	19.0 (29.6)	30	11.1 (23.7)
Cycle 7	38	20.2 (33.4)	28	10.7 (22.3)
Cycle 8	34	18.6 (32.0)	22	13.6 (19.7)
Cycle 9	33	20.2 (26.3)	18	14.8 (28.5)
Cycle 10	29	17.2 (29.0)	14	14.3 (31.3)
Insomnia				
Cycle 1	67	25.4 (29.6)	66	26.3 (27.7)
Cycle 2	69	36.7 (35.8)	67	27.4 (30.7)
Cycle 3	59	35.6 (30.9)	56	24.7 (27.2)
Cycle 4	55	35.2 (33.0)	43	22.5 (24.9)
Cycle 5	48	25.0 (26.2)	41	24.0 (27.4)
Cycle 6	42	31.0 (32.4)	30	28.9 (35.8)
Cycle 7	38	32.9 (35.6)	28	23.2 (29.2)
Cycle 8	34	28.4 (34.9)	22	28.8 (23.7)
Cycle 9	33	26.3 (32.0)	18	29.6 (30.0)
Cycle 10	29	31.0 (34.4)	14	23.8 (24.2)
Nausea and vomiting				
Cycle 1	67	6.7 (12.3)	66	12.6 (22.1)
Cycle 2	69	13.0 (19.6)	67	16.4 (21.8)
Cycle 3	60	15.8 (22.6)	56	15.3 (25.4)
Cycle 4	55	15.8 (21.4)	43	15.1 (24.1)
Cycle 5	48	15.6 (25.1)	41	11.6 (15.9)
Cycle 6	42	11.5 (16.7)	31	14.5 (17.6)
Cycle 7	38	13.8 (19.6)	28	9.5 (16.0)
Cycle 8	34	11.8 (22.3)	22	16.3 (25.0)
Cycle 9	33	9.6 (16.7)	18	6.5 (11.6)
Cycle 10	29	8.6 (14.5)	14	3.6 (9.6)
Pain				
Cycle 1	67	22.9 (24.4)	66	22.5 (28.9)
Cycle 2	69	29.5 (27.6)	67	28.6 (34.5)
Cycle 3	60	28.1 (27.4)	56	28.7 (32.0)
Cycle 4	55	25.5 (27.9)	43	24.0 (28.7)

Table 5. Summary of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Scales - Absolute Scale Scores by Cycle - PRO Analysis Set

Subscale	Sunitinib (N=73)		Placebo (N=71)	
	n	Mean (SD)	n	Mean (SD)
Cycle 5	48	26.7 (25.4)	41	28.0 (32.8)
Cycle 6	42	25.0 (25.6)	31	31.2 (34.1)
Cycle 7	38	23.9 (26.9)	28	23.5 (25.6)
Cycle 8	34	23.0 (26.6)	22	28.0 (33.1)
Cycle 9	33	25.3 (24.7)	18	22.2 (32.8)
Cycle 10	29	17.2 (15.7)	14	26.2 (26.7)

Baseline is defined as Cycle 1.
Range of score by domain/symptom is 0-100.
Higher score on functioning or global health status/QoL scale = better function or better QoL.
Higher score on symptom scale = higher symptomology or more problems.
Visit windows were applied for the EORTC QLQ-C30 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.
N = total number of subjects; n = number of subjects with who completed the scale at the respective cycle; PRO = patient reported outcome; QoL = quality of life; SD = standard deviation.

Table 6. Statistical Analysis of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Scales - PRO Analysis Set

	Estimated Score [a]		
Subscale	Overall Mean Difference	95% CI	p-value
Global quality of life	1.1543	-4.3, 6.6	0.6799
Cognitive functioning	-1.4404	-6.9, 4.0	0.6058
Emotional functioning	-3.5575	-10.3, 3.2	0.3008
Physical functioning	2.7911	-2.8, 8.3	0.3230
Role functioning	1.5113	-6.5, 9.5	0.7113
Social functioning	-1.6672	-8.9, 5.5	0.6487
Appetite loss	1.8800	-6.4, 10.1	0.6545
Constipation	-4.0035	-10.0, 2.0	0.1936
Diarrhea	21.3801	14.3, 28.4	<0.0001
Dyspnea	5.2300	-1.6, 12.1	0.1339
Fatigue	1.7816	-5.1, 8.7	0.6138
Financial difficulties	0.2778	-6.6, 7.1	0.9367
Insomnia	7.7530	0.5, 15	0.0372
Nausea and vomiting	1.1463	-4.6, 6.9	0.6939
Pain	-3.5128	-11.2, 4.2	0.3711

CI = confidence interval; EORTC QLQ = European Organization for Research and Treatment of Cancer quality of life questionnaire; PRO = patient reported outcome.
a. From a repeated measures mixed-effects model with an intercept term, treatment, time from first dose, treatment-by-time interaction, and baseline EORTC QLQ-30 subscale baseline score (intercept and time from first dose are included as random effects)..

Safety Results: An overall summary of treatment-emergent AEs is presented in Table 7.

Table 7. Overall Summary of Treatment-Emergent Adverse Events – As Treated Population

Number (%) of Subjects	Sunitinib		Placebo	
	All Causalities	Treatment-Related	All Causalities	Treatment-Related
Evaluable for AEs	83	83	82	82
Number of AEs	1078	800	703	370
With AEs	82 (98.8)	81 (97.6)	78 (95.1)	64 (78.0)
With SAEs	22 (26.5)	11 (13.3)	34 (41.5)	6 (7.3)
With Grade 3/4 AEs	45 (54.2)	37 (44.6)	41 (50.0)	16 (19.5)
With Grade 5 AEs	4 (4.8)	1 (1.2)	6 (7.3)	1 (1.2)
Discontinued due to AEs	18 (21.7)	10 (12.0)	14 (17.1)	2 (2.4)
Dose reduced due to AEs	19 (22.9)	19 (22.9)	2 (2.4)	2 (2.4)
Temporary discontinuation due to AEs	41 (49.4)	35 (42.2)	26 (31.7)	15 (18.3)

AEs and SAEs are not separated out.
AE = adverse event; SAE = serious adverse event

Treatment-emergent non-serious AEs (all causalities) occurring in ≥5% of subjects in either treatment group are summarized in Table 8.

Table 8. Treatment-Emergent Adverse Events (All Causalities, All Cycles) Occurring in ≥5% Subjects in Either Treatment Group – As Treated Population

Number (%) of Subjects With Preferred Term Adverse Event	Sunitinib (N=83)		Placebo (N=82)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Diarrhoea	49 (59.0)	4 (4.8)	32 (39.0)	2 (2.4)
Nausea	37 (44.6)	1 (1.2)	24 (29.3)	1 (1.2)
Asthenia	28 (33.7)	4 (4.8)	22 (26.8)	3 (3.7)
Vomiting	28 (33.7)	0	25 (30.5)	2 (2.4)
Fatigue	27 (32.5)	4 (4.8)	22 (26.8)	7 (8.5)
Hair color changes	24 (28.9)	1 (1.2)	1 (1.2)	0
Neutropenia	24 (28.9)	10 (12.0)	3 (3.7)	0
Abdominal pain	23 (27.7)	4 (4.8)	26 (31.7)	8 (9.8)
Hypertension	22 (26.5)	8 (9.6)	4 (4.9)	1 (1.2)
Palmar-plantar erythrodysaesthesia syndrome	19 (22.9)	5 (6.0)	2 (2.4)	0
Anorexia	18 (21.7)	2 (2.4)	17 (20.7)	1 (1.2)
Stomatitis	18 (21.7)	3 (3.6)	2 (2.4)	0
Dysgeusia	17 (20.5)	0	4 (4.9)	0
Epistaxis	17 (20.5)	1 (1.2)	4 (4.9)	0
Headache	15 (18.1)	0	11 (13.4)	1 (1.2)
Insomnia	15 (18.1)	0	10 (12.2)	0
Rash	15 (18.1)	0	4 (4.9)	0
Thrombocytopenia	14 (16.9)	3 (3.6)	4 (4.9)	0
Mucosal inflammation	13 (15.7)	1 (1.2)	6 (7.3)	0
Weight decreased	13 (15.7)	1 (1.2)	9 (11.0)	0
Arthralgia	12 (14.5)	0	5 (6.1)	0
Constipation	12 (14.5)	0	16 (19.5)	1 (1.2)
Dry skin	12 (14.5)	0	9 (11.0)	0
Dyspepsia	12 (14.5)	0	5 (6.1)	0
Abdominal pain upper	11 (13.3)	1 (1.2)	6 (7.3)	0
Back pain	10 (12.0)	0	14 (17.1)	4 (4.9)
Dyspnea	10 (12.0)	1 (1.2)	12 (14.6)	1 (1.2)
Edema peripheral	10 (12.0)	0	12 (14.6)	1 (1.2)
Leukopenia	9 (10.8)	5 (6.0)	1 (1.2)	0
Pyrexia	9 (10.8)	1 (1.2)	9 (11.0)	0
Chills	8 (9.6)	0	2 (2.4)	0
Erythema	8 (9.6)	0	4 (4.9)	0
Hypoglycemia	8 (9.6)	4 (4.8)	3 (3.7)	1 (1.2)
Nail disorder	8 (9.6)	0	1 (1.2)	0
Pain in extremity	8 (9.6)	0	6 (7.3)	1 (1.2)
Cough	7 (8.4)	0	7 (8.5)	0
Dry mouth	7 (8.4)	0	5 (6.1)	0
Gingival bleeding	7 (8.4)	0	0	0
Eyelid edema	6 (7.2)	1 (1.2)	0	0
Hypothyroidism	6 (7.2)	0	1 (1.2)	0
Musculoskeletal pain	6 (7.2)	0	8 (9.8)	2 (2.4)
Oropharyngeal pain	6 (7.2)	0	2 (2.4)	0
Urinary tract infection	6 (7.2)	0	3 (3.7)	0
Yellow skin	6 (7.2)	0	0	0
Alopecia	5 (6.0)	0	1 (1.2)	0
Anemia	5 (6.0)	1 (1.2)	8 (9.8)	1 (1.2)
Aphthous stomatitis	5 (6.0)	0	2 (2.4)	0
Chest pain	5 (6.0)	0	5 (6.1)	0
Decreased appetite	5 (6.0)	0	4 (4.9)	0

Table 8. Treatment-Emergent Adverse Events (All Causalities, All Cycles) Occurring in ≥5% Subjects in Either Treatment Group – As Treated Population

Number (%) of Subjects With Preferred Term Adverse Event	Sunitinib (N=83)		Placebo (N=82)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Dizziness	5 (6.0)	1 (1.2)	5 (6.1)	0
Flatulence	5 (6.0)	0	2 (2.4)	0
Hemorrhoids	5 (6.0)	0	0	0
Hypokalemia	5 (6.0)	1 (1.2)	2 (2.4)	0
Muscle spasms	5 (6.0)	0	4 (4.9)	0
Edema	5 (6.0)	0	3 (3.7)	1 (1.2)
Oral pain	5 (6.0)	1 (1.2)	0	0
Pruritis	4 (4.8)	0	9 (11.0)	0
Blood alkaline phosphatase increased	3 (3.6)	0	6 (7.3)	2 (2.4)
Hyperhidrosis	3 (3.6)	0	6 (7.3)	0
Depression	2 (2.4)	0	5 (6.1)	0
Hypoalbuminaemia	2 (2.4)	0	7 (8.5)	1 (1.2)

AEs and SAEs are not separated out.
MedDRA (v12.0) coding dictionary applied.
AE = adverse event; N = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

A summary of treatment-related AEs reported by ≥5% of subjects in either treatment group is provided in Table 9.

Table 9. Treatment-Emergent Adverse Events (Treatment-Related, All Cycles) Occurring in ≥5% Subjects in Either Treatment Group – As Treated Population

Number (%) of Subjects With Preferred Term Adverse Event	Sunitinib (N=83)		Placebo (N=82)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any Adverse events	81 (97.6)		64 (78.0)	
Diarrhoea	44 (53.0)	4 (4.8)	25 (30.5)	1 (1.2)
Nausea	32 (38.6)	1 (1.2)	18 (22.0)	0
Asthenia	26 (31.3)	3 (3.6)	18 (22.0)	2 (2.4)
Fatigue	24 (28.9)	4 (4.8)	14 (17.1)	3 (3.7)
Hair color changes	24 (28.9)	1 (1.2)	1 (1.2)	0
Neutropenia	24 (28.9)	10 (12.0)	3 (3.7)	0
Vomiting	21 (25.3)	0	14 (17.1)	0
Hypertension	19 (22.9)	8 (9.6)	3 (3.7)	0
Palmar-plantar erythrodysaesthesia syndrome	19 (22.9)	5 (6.0)	2 (2.4)	0
Stomatitis	18 (21.7)	3 (3.6)	2 (2.4)	0
Anorexia	17 (20.5)	2 (2.4)	11 (13.4)	0
Dysgeusia	16 (19.3)	0	3 (3.7)	0
Epistaxis	16 (19.3)	1 (1.2)	2 (2.4)	0
Thrombocytopenia	14 (16.9)	3 (3.6)	4 (4.9)	0
Mucosal inflammation	13 (15.7)	1 (1.2)	6 (7.3)	0
Rash	13 (15.7)	0	4 (4.9)	0
Abdominal pain	12 (14.5)	1 (1.2)	10 (12.2)	3 (3.7)
Dyspepsia	12 (14.5)	0	1 (1.2)	0
Weight decreased	11 (13.3)	1 (1.2)	6 (7.3)	0
Dry skin	11 (13.3)	0	9 (11.0)	0
Headache	10 (12.0)	0	5 (6.1)	1 (1.2)
Constipation	8 (9.6)	0	8 (9.8)	1 (1.2)
Leukopenia	8 (9.6)	5 (6.0)	1 (1.2)	0
Nail disorder	8 (9.6)	0	1 (1.2)	0
Dry mouth	7 (8.4)	0	4 (4.9)	0
Erythema	7 (8.4)	0	3 (3.7)	0
Insomnia	7 (8.4)	0	5 (6.1)	0
Pain in extremity	7 (8.4)	0	3 (3.7)	0
Abdominal pain upper	6 (7.2)	1 (1.2)	1 (1.2)	0
Arthralgia	6 (7.2)	0	2 (2.4)	0
Dyspnea	6 (7.2)	1 (1.2)	8 (9.8)	0
Yellow skin	6 (7.2)	0	0	0
Alopecia	5 (6.0)	0	1 (1.2)	0
Aphthous stomatitis	5 (6.0)	0	2 (2.4)	0
Decreased appetite	5 (6.0)	0	3 (3.7)	0
Dizziness	5 (6.0)	1 (1.2)	3 (3.7)	0
Eyelid edema	5 (6.0)	1 (1.2)	0	0
Flatulence	5 (6.0)	0	1 (1.2)	0
Gingival bleeding	5 (6.0)	0	0	0
Hypothyroidism	5 (6.0)	0	1 (1.2)	0
Pruritus	4 (4.8)	0	7 (8.5)	0
Oedema peripheral	3 (3.6)	0	5 (6.1)	0
Hyperhidrosis	2 (2.4)	0	6 (7.3)	0

AEs and SAEs are not separated out.
MedDRA (v12.0) coding dictionary applied.
AE = adverse event; N = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Serious Adverse Events (SAEs): Treatment-emergent SAEs (all causalities) are summarized by system organ class and preferred term in Table 10.

All-causality SAEs were more commonly reported in subjects receiving placebo (41.5%) compared to sunitinib (26.5%), and these were most frequently gastrointestinal disorders (10.8% of sunitinib subjects and 14.6% of placebo subjects). Disease progression was the most common SAE on the sunitinib arm (3.6% compared to 2.4% of placebo subjects). Diarrhea, which was the most common AE, was reported as an SAE for 1 subject (1.2%) on the sunitinib arm. Hypoglycemia, an AE of special interest for sunitinib was reported as an SAE for 2 subjects (2.4%) on the placebo arm.

Table 10. Treatment-Emergent Serious Adverse Events (All Causalities, All Cycles) - As Treated Population

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Any AEs	22 (26.5)	34 (41.5)
Blood and lymphatic system disorders	2 (2.4)	0
Anaemia	1 (1.2)	0
Leukopenia	1 (1.2)	0
Neutropenia	1 (1.2)	0
Thrombocytopenia	1 (1.2)	0
Cardiac disorders	2 (2.4)	0
Cardiac failure	2 (2.4)	0
Ventricular arrhythmia	1 (1.2)	0
Eye disorders	1 (1.2)	0
Eye disorder	1 (1.2)	0
Gastrointestinal disorders	9 (10.8)	12 (14.6)
Abdominal pain	2 (2.4)	4 (4.9)
Abdominal pain upper	2 (2.4)	0
Ascites	1 (1.2)	0
Diarrhoea	1 (1.2)	0
Duodenal ulcer	1 (1.2)	1 (1.2)
Duodenal ulcer perforation	0	1 (1.2)
Erosive duodenitis	0	1 (1.2)
Haematemesis	0	2 (2.4)
Ileus	0	1 (1.2)
Mallory-Weiss syndrome	1 (1.2)	0
Melaena	0	2 (2.4)
Nausea	2 (2.4)	1 (1.2)
Pancreatitis	1 (1.2)	0
Pancreatitis acute	0	1 (1.2)
Rectal haemorrhage	0	1 (1.2)
Varices oesophageal	1 (1.2)	0
Vomiting	2 (2.4)	3 (3.7)
General disorders and administration site conditions	7 (8.4)	8 (9.8)
Asthenia	0	1 (1.2)
Disease progression	3 (3.6)	2 (2.4)
Fatigue	1 (1.2)	1 (1.2)
General physical health deterioration	1 (1.2)	2 (2.4)
Hyperthermia	1 (1.2)	0
Inflammation	0	1 (1.2)
Mucosal inflammation	1 (1.2)	0
Multi-organ failure	0	1 (1.2)
Oedema	0	1 (1.2)
Oedema peripheral	0	1 (1.2)
Pyrexia	1 (1.2)	2 (2.4)
Hepatobiliary disorders	3 (3.6)	5 (6.1)
Bile duct obstruction	1 (1.2)	0
Cholangitis	0	1 (1.2)
Hepatic failure	0	2 (2.4)
Hepatic function abnormal	1 (1.2)	0
Hepatic pain	1 (1.2)	2 (2.4)
Infections and infestations	3 (3.6)	2 (2.4)
Anal abscess	1 (1.2)	0

Table 10. Treatment-Emergent Serious Adverse Events (All Causalities, All Cycles) - As Treated Population

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Catheter related infection	1 (1.2)	0
Liver abscess	0	1 (1.2)
Pneumonia	0	1 (1.2)
Varicella	1 (1.2)	0
Injury, poisoning and procedural complications	1 (1.2)	6 (7.3)
Accident	0	1 (1.2)
Facial bones fracture	0	1 (1.2)
Humerus fracture	0	1 (1.2)
Joint sprain	0	1 (1.2)
Road traffic accident	0	1 (1.2)
Spinal compression fracture	1 (1.2)	0
Stent occlusion	0	1 (1.2)
Therapeutic agent toxicity	0	1 (1.2)
Traumatic brain injury	0	1 (1.2)
Investigations	1 (1.2)	1 (1.2)
Haemoglobin decreased	0	1 (1.2)
Lipase increased	1 (1.2)	0
Metabolism and nutrition disorders	1 (1.2)	5 (6.1)
Acidosis	0	1 (1.2)
Dehydration	0	1 (1.2)
Hypercalcaemia	0	1 (1.2)
Hyperkalaemia	1 (1.2)	0
Hypoglycaemia	0	2 (2.4)
Musculoskeletal and connective tissue disorders	1 (1.2)	3 (3.7)
Back pain	0	2 (2.4)
Bone pain	1 (1.2)	0
Neck pain	0	1 (1.2)
Pain in extremity	0	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.2)
Malignant pleural effusion	0	1 (1.2)
Nervous system disorders	4 (4.8)	4 (4.9)
Cerebral haematoma	1 (1.2)	0
Cerebrovascular accident	0	1 (1.2)
Convulsion	0	1 (1.2)
Headache	1 (1.2)	0
Hepatic encephalopathy	1 (1.2)	1 (1.2)
Leukoencephalopathy	1 (1.2)	0
Somnolence	0	1 (1.2)
Renal and urinary disorders	2 (2.4)	1 (1.2)
Renal failure	2 (2.4)	0
Renal failure acute	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	3 (3.7)
Dyspnoea	1 (1.2)	0
Haemoptysis	1 (1.2)	0
Pleurisy	0	1 (1.2)
Pulmonary embolism	0	2 (2.4)
Vascular disorders	1 (1.2)	3 (3.7)
Deep vein thrombosis	0	1 (1.2)
Hypertension	1 (1.2)	0

Table 10. Treatment-Emergent Serious Adverse Events (All Causalities, All Cycles) - As Treated Population

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Hypotension	0	2 (2.4)

MedDRA (v12.0) coding dictionary applied.
AE = adverse event; N = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities.

A summary of treatment-emergent SAEs (treatment related) occurring in any treatment arm is provided in Table 11.

Table 11. Treatment-Emergent Serious Adverse Events (Treatment Related, All Cycles) - As Treated Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Any Adverse events	11 (13.3)	6 (7.3)
Blood and lymphatic system disorders	1 (1.2)	0
Leukopenia	1 (1.2)	0
Neutropenia	1 (1.2)	0
Thrombocytopenia	1 (1.2)	0
Cardiac disorders	1 (1.2)	0
Cardiac failure	1 (1.2)	0
Ventricular arrhythmia	1 (1.2)	0
Gastrointestinal disorders	5 (6.0)	1 (1.2)
Abdominal pain	1 (1.2)	1 (1.2)
Abdominal pain upper	2 (2.4)	0
Diarrhoea	1 (1.2)	0
Duodenal ulcer	1 (1.2)	0
Mallory-Weiss syndrome	1 (1.2)	0
Nausea	2 (2.4)	0
Vomiting	1 (1.2)	0
General disorders and administration site conditions	2 (2.4)	1 (1.2)
Fatigue	1 (1.2)	0
Mucosal inflammation	1 (1.2)	0
Pyrexia	0	1 (1.2)
Hepatobiliary disorders	2 (2.4)	0
Bile duct obstruction	1 (1.2)	0
Hepatic function abnormal	1 (1.2)	0
Infections and infestations	1 (1.2)	1 (1.2)
Anal abscess	1 (1.2)	0
Pneumonia	0	1 (1.2)
Metabolism and nutrition disorders	1 (1.2)	2 (2.4)
Dehydration	0	1 (1.2)
Hyperkalaemia	1 (1.2)	0
Hypoglycaemia	0	1 (1.2)
Musculoskeletal and connective tissue disorders	0	1 (1.2)
Back pain	0	1 (1.2)
Nervous system disorders	2 (2.4)	0
Cerebral haematoma	1 (1.2)	0
Leukoencephalopathy	1 (1.2)	0
Renal and urinary disorders	2 (2.4)	0
Renal failure	2 (2.4)	0
Respiratory, thoracic and mediastinal disorders	1 (1.2)	2 (2.4)
Dyspnoea	1 (1.2)	0
Haemoptysis	1 (1.2)	0
Pleurisy	0	1 (1.2)
Pulmonary embolism	0	1 (1.2)
Vascular disorders	1 (1.2)	1 (1.2)
Deep vein thrombosis	0	1 (1.2)
Hypertension	1 (1.2)	0

MedDRA (v12.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of subjects

Permanent Discontinuations due to Adverse Events: A summary of treatment-emergent all-causality AEs leading to permanent discontinuation in subjects is provided in Table 12.

Table 12. Summary of Discontinuations due to Treatment-Emergent Adverse Events (All Causalities, All Cycles) - As Treated Population

Number (%) of subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Any Adverse events	18 (21.7)	14 (17.1)
Blood and lymphatic system disorders	1 (1.2)	0
Neutropenia	1 (1.2)	0
Cardiac disorders	3 (3.6)	0
Cardiac failure	2 (2.4)	0
Cardiomyopathy	1 (1.2)	0
Gastrointestinal disorders	3 (3.6)	3 (3.7)
Abdominal pain	0	2 (2.4)
Ascites	1 (1.2)	0
Diarrhoea	2 (2.4)	0
Nausea	0	1 (1.2)
Vomiting	0	1 (1.2)
General disorders and administration site conditions	8 (9.6)	5 (6.1)
Asthenia	1 (1.2)	0
Disease progression	3 (3.6)	3 (3.7)
Fatigue	3 (3.6)	1 (1.2)
General physical health deterioration	0	1 (1.2)
Mucosal inflammation	1 (1.2)	0
Hepatobiliary disorders	2 (2.4)	2 (2.4)
Bile duct obstruction	1 (1.2)	0
Hepatic failure	0	2 (2.4)
Hyperbilirubinaemia	1 (1.2)	0
Infections and infestations	1 (1.2)	0
Catheter related infection	1 (1.2)	0
Injury, poisoning and procedural complications	1 (1.2)	0
Spinal compression fracture	1 (1.2)	0
Metabolism and nutrition disorders	0	1 (1.2)
Dehydration	0	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.2)
Malignant pleural effusion	0	1 (1.2)
Nervous system disorders	2 (2.4)	3 (3.7)
Cerebrovascular accident	0	1 (1.2)
Convulsion	0	1 (1.2)
Hepatic encephalopathy	1 (1.2)	0
Leukoencephalopathy	1 (1.2)	0
Tremor	0	1 (1.2)
Vascular disorders	1 (1.2)	0
Hypertension	1 (1.2)	0

MedDRA (v12.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects.

Dose Reductions or Temporary Discontinuations due to Adverse Events: A summary of treatment-emergent all-causality AEs leading to temporary discontinuation or dose reduction in subjects is provided in Table 13.

Table 13. Temporary Discontinuations or Dose Reductions due to Treatment-Emergent Adverse Events (All Causalities, All Cycles) - As Treated Population

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Any Adverse events	45 (54.2)	27 (32.9)
Blood and lymphatic system disorders	12 (14.5)	0
Leukopenia	3 (3.6)	0
Neutropenia	10 (12.0)	0
Thrombocytopenia	5 (6.0)	0
Endocrine disorders	1 (1.2)	0
Hypothyroidism	1 (1.2)	0
Eye disorders	2 (2.4)	0
Eye disorder	1 (1.2)	0
Eyelid oedema	1 (1.2)	0
Gastrointestinal disorders	19 (22.9)	12 (14.6)
Abdominal distension	0	1 (1.2)
Abdominal pain	2 (2.4)	3 (3.7)
Abdominal pain upper	1 (1.2)	0
Anal inflammation	1 (1.2)	0
Diarrhoea	8 (9.6)	1 (1.2)
Duodenal ulcer	1 (1.2)	1 (1.2)
Erosive duodenitis	0	1 (1.2)
Faeces discoloured	0	1 (1.2)
Gingivitis	0	1 (1.2)
Mallory-Weiss syndrome	1 (1.2)	0
Nausea	4 (4.8)	2 (2.4)
Oral pain	2 (2.4)	0
Pancreatitis acute	0	1 (1.2)
Rectal haemorrhage	0	1 (1.2)
Stomatitis	5 (6.0)	0
Toothache	1 (1.2)	1 (1.2)
Varices oesophageal	1 (1.2)	0
Vomiting	2 (2.4)	3 (3.7)
General disorders and administration site conditions	13 (15.7)	8 (9.8)
Asthenia	7 (8.4)	4 (4.9)
Chills	1 (1.2)	0
Fatigue	2 (2.4)	1 (1.2)
General physical health deterioration	0	1 (1.2)
Mucosal inflammation	2 (2.4)	1 (1.2)
Oedema	1 (1.2)	1 (1.2)
Pyrexia	2 (2.4)	1 (1.2)
Hepatobiliary disorders	1 (1.2)	2 (2.4)
Hepatic pain	0	1 (1.2)
Hyperbilirubinaemia	0	1 (1.2)
Jaundice	1 (1.2)	0
Infections and infestations	3 (3.6)	4 (4.9)
Enterocolitis infectious	0	1 (1.2)
Gastroenteritis	0	1 (1.2)
Liver abscess	0	1 (1.2)
Pneumonia	0	1 (1.2)
Tooth abscess	1 (1.2)	0
Upper respiratory tract infection	1 (1.2)	1 (1.2)

Table 13. Temporary Discontinuations or Dose Reductions due to Treatment-Emergent Adverse Events (All Causalities, All Cycles) - As Treated Population

Number (%) of Subjects by System Organ Class and Preferred Term	Sunitinib (N=83)	Placebo (N=82)
Varicella	1 (1.2)	0
Injury, poisoning and procedural complications	1 (1.2)	1 (1.2)
Heat stroke	1 (1.2)	0
Therapeutic agent toxicity	0	1 (1.2)
Investigations	4 (4.8)	1 (1.2)
Blood bilirubin increased	1 (1.2)	0
Blood thyroid stimulating hormone increased	1 (1.2)	0
Neutrophil count decreased	2 (2.4)	0
Weight decreased	0	1 (1.2)
Metabolism and nutrition disorders	3 (3.6)	4 (4.9)
Anorexia	1 (1.2)	1 (1.2)
Cachexia	1 (1.2)	0
Dehydration	0	1 (1.2)
Hypercalcaemia	0	1 (1.2)
Hyperglycaemia	0	1 (1.2)
Hyperkalaemia	0	1 (1.2)
Hypoglycaemia	0	1 (1.2)
Hypokalaemia	1 (1.2)	0
Nervous system disorders	1 (1.2)	1 (1.2)
Dizziness	0	1 (1.2)
Neuropathy peripheral	1 (1.2)	0
Psychiatric disorders	0	1 (1.2)
Agitation	0	1 (1.2)
Confusional state	0	1 (1.2)
Renal and urinary disorders	1 (1.2)	1 (1.2)
Renal failure	1 (1.2)	0
Renal failure acute	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders	5 (6.0)	6 (7.3)
Dyspnoea	1 (1.2)	2 (2.4)
Dyspnoea exertional	1 (1.2)	0
Epistaxis	1 (1.2)	0
Haemoptysis	1 (1.2)	1 (1.2)
Nasal mucosal disorder	1 (1.2)	0
Pleurisy	0	1 (1.2)
Pulmonary embolism	0	2 (2.4)
Skin and subcutaneous tissue disorders	11 (13.3)	1 (1.2)
Hyperhidrosis	1 (1.2)	0
Hyperkeratosis	1 (1.2)	0
Palmar-plantar erythrodysaesthesia syndrome	8 (9.6)	0
Swelling face	1 (1.2)	1 (1.2)
Vascular disorders	7 (8.4)	1 (1.2)
Haematoma	0	1 (1.2)
Hypertension	7 (8.4)	0

MedDRA (v12.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects.

Death: Deaths are summarized in Table 14 (As Treated population). The incidence of death was higher on the placebo arm (21/82 subjects, 25.6%) as compared to the sunitinib arm

(9/83 subjects, 10.8%). Most deaths were due to the disease under study; none of the deaths were considered to be related to study treatment.

Table 14. Summary of Deaths – As Treated Population

Number (%) of Subjects	Sunitinib (N=83)	Placebo (N=82)
Deaths	9 (10.8)	21 (25.6)
Subjects who died while on study[a]	5 (6.0)	9 (11.0)
Disease under study	4 (4.8)	7 (8.5)
Study treatment toxicity	1 (1.2)[b]	1 (1.2)[c]
Other	0	1 (1.2)[d]
Subjects who died during follow-up[e]	4 (4.8)	12 (14.6)
Disease under study	3 (3.6)	12 (14.6)
Study treatment toxicity	0	0
Other	1 (1.2)[f]	0

N = number of subjects.
a. On study deaths are those that occurred after the first dose of study drug and within 28 days of last dose of study medication.
b. Heart failure.
c. Dehydration.
d. Hepatic failure.
e. Follow-up deaths are those that occurred more than 28 days after last dose of study medication.
f. Cardiac insufficiency.

Clinical Laboratory Results and Other Safety Findings:

Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 hematology abnormalities were more common for the sunitinib arm compared to the placebo arm (Table 15). These abnormalities represented shifts from CTCAE Grade ≤2 to Grade ≥3, with the exception of Grade 3 lymphocyte abnormality in 1 subject on the sunitinib arm, which was also Grade 3 at baseline.

Table 15. Summary of CTCAE Grade 3 and 4 Hematology Abnormalities (All Cycles) – As Treated Population

	Number (%) of Subjects With Abnormality			
	Sunitinib (N=82)		Placebo (N=80)	
Parameter	Grade 3	Grade 4	Grade 3	Grade 4
Hemoglobin	0	0	1 (1.3)	0
Platelets	3 (3.7)	1 (1.2)	0	0
Neutrophils (absolute)	11 (13.4)	2 (2.4)	0	0
White blood cells	7 (8.5)	0	0	0
Lymphocytes (absolute)	6 (7.3)[a]	0	3 (3.8)	0

CTCAE = Common Terminology Criteria for Adverse Events; N = number of subjects.
a. Abnormality was also Grade 3 at Baseline for 1 of these subjects.

When measured during Cycles 2-5, mean changes from baseline in systolic and diastolic blood pressure were more marked for the sunitinib arm compared to the placebo arm; on the sunitinib arm, there was a mean increase of 6.3-12.5 mmHg in systolic blood pressure compared to mean decreases or increases <1 mmHg on the placebo arm. For the absolute values, 43.8% of evaluated sunitinib subjects had maximum systolic blood pressure

>150 mmHg and/or maximum diastolic blood pressure >100 mmHg compared to 25.0% of evaluated placebo subjects, and 10.0% of evaluated sunitinib subjects had systolic blood pressure >200 mmHg and/or diastolic blood pressure >110 mmHg compared to 2.6% of evaluated placebo subjects.

One subject (on the sunitinib arm) had a QTc interval ≥500 msec during Cycle 3 (519 msec), and this QTc interval prolongation was recorded as a CTCAE Grade 3/4 abnormality. The prolonged QTc interval was measured during an unplanned ECG reading on Day 68; the subject was hospitalized on that day and experienced a number of SAEs, including ventricular arrhythmia and cardiac failure, and the subject died.

CONCLUSIONS:

Sunitinib 37.5 mg on a continuous daily dosing schedule resulted in a clinically significant improvement in PFS as compared to placebo in the treatment of subjects with progressive, well-differentiated pancreatic islet cell tumors, with a median PFS of 11.4 months vs 5.5 months (hazard ratio 0.418, p=0.0001, 81 PFS events).

Sunitinib treatment was associated with longer survival as compared to placebo, with a hazard ratio for OS of 0.409 (95% CI: 0.187, 0.894; p=0.0204, 30 OS events).

Sunitinib treatment resulted in a clinically and statistically significant increase in Investigator-assessed ORR as compared to placebo (9.3% vs. 0%; 95% CI: 3.2, 15.4; p=0.0066); median TTR and DR could not be estimated.

The adverse events reported in sunitinib-treated subjects were generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy.

Global health-related quality of life and functioning domains were maintained for subjects on sunitinib treatment with limited adverse symptomatic effects.