

**PFIZER INC**

**SUTENT<sup>®</sup> (sunitinib malate) Capsules**

**For the Treatment of Unresectable Pancreatic Neuroendocrine  
Tumors**

**(NDA 21-938/S-013)**

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## LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
AE	Adverse Event
ALT	Alanine aminotransferase
AM	Ante Meridiem
ANC	Absolute Neutrophil Count
APUD	Amine precursor uptake and decarboxylation
AST	Aspartate aminotransferase
AT	As-Treated
ATP	Adenosine Triphosphate
AUC	Area Under the Plasma-Concentration – Time curve
AUC <sub>∞</sub>	Area Under the Plasma-Concentration – Time curve from 0 to infinity
AUC <sub>24</sub>	Area Under the Plasma-Concentration – Time curve from 0 to 24 hours
BICR	Blinded Independent Central Review
BP	Blood pressure
BUN	Blood urea nitrogen
CDD	Continuous Daily Dosing
CgA	chromogranin A
CI	Confidence Interval
CR	Complete Response
CRFs	Case Report Forms
CSF-1R	Colony Stimulating Factor-1 Receptor
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C <sub>trough</sub>	Trough Plasma Concentration
CV	Coefficient of Variation

DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol Group EQ-5D Self-Report
EQ-VAS	EQ-5D Visual Analog Scale
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FLT-3	Fms-like tyrosine kinase-3 receptor
G	Gastrin
GIST	Gastrointestinal Stromal Tumor
HIF	Hypoxia Inducible Factor
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
ITT	Intent-to-Treat
KIT	Stem Cell Factor Receptor
LC/MS/MS	High-performance liquid chromatography/mass spectrometry/mass spectrometry
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MEN1	Multiple Endocrine Neoplasia type 1
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
NDA	New Drug Application

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NET	Neuroendocrine Tumors
NMR	Nuclear Magnetic Resonance
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-Free Survival
PK	Pharmacokinetics
PM	Post Meridien
PP	Pancreatic polypeptide
PR	Partial Response
PRO	Patient-reported Outcome
PRRT	Peptide Receptor Radionuclide Therapy
PT	Preferred Term
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RIP	Rat Insulin Promoter
RTK	Receptor Tyrosine Kinase
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SD	Stable Disease or Standard Deviation
SEER	Surveillance, Epidemiology and End Results
SLD	Sum of the Longest Diameters

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sNDA	Supplemental New Drug Application
SOC	System Organ Class
SS	Somatostatin
sVEGFR-2	Soluble Vascular Endothelial Growth Factor Receptor 2
sVEGFR-3	Soluble Vascular Endothelial Growth Factor Receptor 3
Tag	T antigen transgene
TCR	Tumor Control Rate
Total Drug	Sunitinib + SU012662
TSH	Thyroid-stimulating hormone
TSTM	Too Small to Measure
TTF	Time to Treatment Failure
TTP	Time to Tumor Progression
TTR	Time to Tumor Response
ULN	Upper limit of normal
VAS	Visual Analog Scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VIP	Vasoactive Intestinal Peptide
VIPoma	Vasoactive intestinal polypeptide tumor
VHL	von Hippel-Lindau
WBC	White blood cell
WHO	World Health Organization

## EXECUTIVE SUMMARY

Unresectable, well-differentiated pancreatic islet cell tumor (also known as pancreatic NET) is a disease with limited therapeutic options; no new treatments have been approved in nearly three decades. Although rare, the reported incidence of pancreatic NET is rising. It is reported in two to four people per million annually worldwide and accounts for approximately nine percent of neuroendocrine tumors. For patients with pancreatic NET that is metastatic, prognosis is poor, similar to that seen with metastatic breast cancer or colon cancer. The efficacy and safety results of sunitinib in Phase II and III studies present a clinically important advancement for the treatment of this serious disease which has a high unmet medical need. The principal evidence for the clinical efficacy and safety of sunitinib in patients with pancreatic NET is derived from 2 studies: a pivotal Phase III Study A6181111, and a supportive Phase II Study RTKC-0511-015.

Pivotal Phase III Study A6181111 was a randomized, double-blind, placebo-controlled, multinational trial of sunitinib in subjects with progressive, well-differentiated pancreatic NET with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST). The primary endpoint was progression-free survival (PFS), and the secondary efficacy endpoints included overall survival (OS), objective response rate (ORR), time to tumor response (TTR), and duration of response (DR). Tumor response and disease progression were assessed by investigators' according to RECIST. The dose of sunitinib was 37.5 mg on a continuous daily dosing (CDD) schedule. An independent Data Monitoring Committee (DMC) was established to monitor the safety of the subjects on an ongoing basis and to evaluate the efficacy data at the pre-specified interim analysis. The study was designed with an interim analysis of 130 PFS events and a final analysis of 260 PFS events. Based on a review of safety in February 2009, the DMC recommended that the study be closed after 73 PFS events as there was a favorable benefit/risk for sunitinib compared with placebo. This recommendation was based on greater PFS observed in the sunitinib arm and the observation of a higher number of deaths and serious adverse events in the placebo arm. The study sponsor accepted the DMC recommendation and notified investigators in March 2009 that the study would be closed and remaining subjects were offered sunitinib on 1 of 2 open-label extension studies. The last subject visit in Study A6181111 occurred on 15 April 2009. Included in this Briefing Document are the efficacy data based on 171 subjects enrolled on Study A6181111.

Supportive Phase II Study RTKC-0511-015 was an open-label, 2-cohort, 2-stage, multicenter study in subjects with unresectable neuroendocrine tumors, including carcinoid tumors (carcinoid tumor cohort) and pancreatic islet cell tumors (pancreatic NET cohort). The efficacy data from the 66 subjects enrolled in the pancreatic NET cohort are included in this document. Efficacy endpoints included ORR, TTR, DR, time to tumor progression (TTP), and OS. Tumor response was assessed by investigators according to RECIST. Subjects received sunitinib 50 mg once daily on Schedule 4/2 (4 weeks on treatment followed by a 2-week off-treatment period per 6-week cycle).

Data from these studies demonstrate that sunitinib is an effective treatment for patients with pancreatic NET. In the pivotal Phase III study A6181111, a clear, clinically significant

improvement in PFS was demonstrated in subjects treated with sunitinib compared to subjects treated with placebo. Sunitinib more than doubled PFS compared with placebo, 11.4 months vs 5.5 months (hazard ratio [HR] = 0.418; 95% CI: 0.263 - 0.662;  $P = 0.000118$ ) according to investigator assessment of response. Upon the request of the US Food and Drug Administration, PFS was subsequently re-analyzed, first using investigator-reported tumor lesion measurements (algorithmic assessment), which demonstrated a median PFS of 12.6 months in the sunitinib arm and 5.4 months in the placebo arm (HR = 0.401; 95% CI: 0.252 - 0.640;  $P = 0.000066$ ) and secondly, by blinded, independent radiographic review, which yielded a median PFS of 12.6 months in the sunitinib arm and 5.8 months in the placebo arm (HR = 0.315; 95% CI: 0.181 - 0.546;  $P = 0.000015$ ). These analyses are consistent with the primary findings, confirming the robustness of the data and the benefit of sunitinib in these patients.

An advantage for sunitinib was also observed in the secondary endpoints of ORR and OS. Eight objective responses (ORs) in the sunitinib arm and no responses in placebo arm were reported for investigator overall assessment; the ORR was 9.3% vs. 0 for the two treatment arms, respectively (95% CI: 3.2 - 15.4,  $P = 0.0066$ ). The ORR by algorithmic assessment was the same, with 8 ORs in the sunitinib arm and 0 in the placebo arm. The ORR in the sunitinib arm may have been an underestimation due to the early termination of the study, which resulted in discontinuation of tumor response evaluation in subjects who were recently enrolled, or who remained on-study without evidence of disease progression at the time of study termination. Among the subjects with an OR, the TTR for the sunitinib arm was 3.1 months (range: 0.8-11.1 months) based on investigator's overall assessment and 2.2 months (range: 0.8-5.6 months) based on algorithmic assessment. Of 8 subjects with an OR, only 1 subject had progressive disease (PD) prior to study termination; the remaining 7 subjects had ongoing tumor responses ranging from 0.9+ to 15+ months.

Kaplan-Meier analysis of OS also demonstrated an advantage for sunitinib treatment. At the time of study closure, the observed hazard ratio for OS was 0.409 (95% CI: 0.187 - 0.894;  $P = 0.0204$ ) and favored sunitinib treatment over placebo treatment, despite crossover of patients randomized to the placebo arm who developed disease progression. Subsequent OS analyses after study termination and crossover of patients without disease progression continued to favor sunitinib treatment.

Clinical activity observed in the Phase II study RTKC-0511-015 was supportive of the results from the pivotal study; PRs were observed in 11 of 66 subjects (ORR 16.7%; 95% CI: 8.6, 27.9) and the median TTP was 7.8 months (95% CI: 6.6 - 12.6) among subjects with an OR. Median OS was not reached in this study.

The safety results from these two studies also support the use of sunitinib for the treatment of pancreatic NET. The most common sunitinib-related adverse events (AEs) were consistent with the known safety profile of sunitinib and/or signs and symptoms of pancreatic NET. Adverse events were most commonly associated with the Gastrointestinal disorders SOC or General disorders and administration site conditions SOC. Treatment-related skin and subcutaneous tissue disorders were also common. Common AEs were generally constitutional (fatigue, anorexia, headache, flushing, cough, pyrexia, and chills), gastrointestinal (diarrhea, nausea, abdominal pain, vomiting, glossodynia, stomatitis,

constipation, dyspepsia, oral pain, and flatulence), cutaneous (rash, skin discoloration, hair color changes, and palmar-plantar erythrodysesthesia syndrome), or blood related (neutropenia, thrombocytopenia, and anemia). Other common AEs not included in these categories were dysgeusia, myalgia, dyspnea, insomnia, pain in extremity, dizziness, arthralgia, paresthesia, edema peripheral, dehydration, back pain, hypertension, periorbital edema, and nasopharyngitis. Most of these AEs were grade 1 or 2 in severity. In the Phase III study, grade 3/4 AEs were more commonly associated with sunitinib treatment. The most frequent treatment-related Grade 3/4 AEs were neutropenia, hypertension, leukopenia, and palmar-plantar erythrodysesthesia syndrome. There were no sunitinib-related events of hepatic failure in either the Phase II or Phase III study. Other significant AEs of particular interest (such as severe AEs of cardiac dysfunction, thyroid dysfunction, hemorrhagic events, thromboembolic events, and hypoglycemia) were of relatively low incidence and did not reveal any new safety risks in either the Phase II or III study. AEs were generally manageable through the use of dosing interruptions, dose reductions, and/or standard medical therapy.

In the Phase III Study A6181111, temporary discontinuations or dose reductions due to AEs occurred more frequently on the sunitinib arm than on the placebo arm (54.2% vs. 32.9%). Gastrointestinal disorders were the most common SOC of AEs leading to temporary discontinuations or dose reductions in the sunitinib arm. These dosing interruptions and dose reductions allowed sunitinib-treated subjects to remain in the study and continue receiving effective treatment, as reflected in the longer median duration of treatment for sunitinib-treated subjects compared to placebo-treated subjects (141 days vs. 113 days) and by the comparable permanent discontinuation rate due to AEs between the two treatment arms, 18 (21.7%) on sunitinib vs. 14 (17.1%) on placebo.

Serious Adverse Events (SAEs) were reported more frequently in the placebo arm than in the sunitinib arm (41.5% vs. 26.5%) and treatment-related SAEs were reported in 13.3% of the sunitinib arm and 7.3% in the placebo arm. These differences were not adjusted for length of time on study, which was longer in the sunitinib arm. Deaths were also reported more frequently in the placebo arm compared to the sunitinib arm (25.6% vs. 10.8%). Most deaths in both treatment arms were considered to have been due to pancreatic NET (or the disease under study). Two deaths, 1 on the sunitinib arm (cardiac failure) and 1 on the placebo arm (dehydration), were considered related to study treatment.

In the Phase II study, four (3.7%) subjects discontinued the study because of AEs secondary to disease progression and not related to the study drug, 5 (4.7%) subjects discontinued because of AEs related to the study drug, and 3 (2.8%) subjects discontinued due to AEs related to neither the study drug nor study disease. This low rate of discontinuations due to AEs (especially those unrelated to disease progression) supports the conclusion that sunitinib treatment was tolerated with manageable toxicities.

The safety profile of sunitinib 37.5 mg CDD in subjects with pancreatic NET was similar to the known safety profile for sunitinib described in the current label for sunitinib 50 mg Schedule 4/2 for advanced renal cell carcinoma (RCC) and imatinib-refractory or intolerant Gastrointestinal Stromal Tumor (GIST). In addition, although more AEs were reported with

sunitinib, fewer SAEs and fewer deaths were associated with sunitinib treatment than with placebo in the Phase III study of pancreatic NET.

Pharmacology data show that the steady state trough plasma exposures to sunitinib and its active metabolite SU012662 in the pancreatic NET subpopulation appear to be similar to that in patients with GIST) and advanced RCC, indicating that the pharmacokinetics (PK) of sunitinib and SU012662 were not tumor type-dependent. The PK of sunitinib and SU012662 appears to be similar between Schedules CDD and 4/2 in GIST and RCC subjects. Therefore, it is projected that the total plasma exposure to sunitinib and SU012662 following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2, and supports the selection of sunitinib 37.5 mg dose on a CDD schedule for supplemental registration in pancreatic NET.

In summary, sunitinib, dosed at 37.5 mg dose on a CDD schedule resulted in a favorable benefit/risk profile in patients with unresectable pancreatic NET, a population with limited treatment options and significant unmet medical need. Treatment with sunitinib yielded more than double the median PFS compared to treatment with placebo (11.4 vs. 5.5 months; HR = 0.418; 95% CI 0.263, 0.662;  $P = 0.000118$ ) translating into more than a 50% reduction in the relative risk of disease progression or death from any cause in subjects with pancreatic NET. An advantage in OS (HR = 0.409; 95% CI 0.187, 0.894;  $P = 0.0204$ ) was also observed for sunitinib treatment.

The safety profile of sunitinib 37.5 mg CDD in subjects with pancreatic NET was similar to the known safety profile for sunitinib described in the current label for sunitinib 50 mg Schedule 4/2 for advanced Renal Cell Carcinoma (RCC) and imatinib-refractory or intolerant Gastrointestinal Stromal Tumor (GIST). In addition, although more AEs were reported with sunitinib, fewer SAEs and fewer deaths were associated with sunitinib treatment than with placebo in the Phase III study in patients with pancreatic NET. Together the safety and efficacy data support the favorable benefit/risk profile for sunitinib in this population.

## 1. INTRODUCTION

### 1.1. Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (NET) are a group of rare tumors of the endocrine pancreas. These tumors are also known as pancreatic islet cell tumors, malignant neoplasms of Islets of Langerhans (ICD-9), and gastroenteropancreatic (GEP)-neuroendocrine tumors (2000 and 2010 WHO classification).<sup>1</sup> They are separate and distinct from neuroendocrine tumors which arise from other sites (e.g. lung, thymus, or other parts of the GI tract), and pancreatic NET are not described as carcinoid tumors, a term which is falling out of favor. These tumors may be functional, in which case they can be referred to by the hormone they secrete (e.g., insulinoma, gastrinoma, glucagonoma, or vasoactive intestinal peptidoma [VIPoma]) or they may be non-functional (i.e., they do not produce symptoms related to hormone secretion).

**Table 1: Nomenclature and Classification of Neuroendocrine Tumors<sup>2-4</sup>**

Classification of NET					
Differentiation and Grade	Mitotic Count *	Ki-67 Index †	Traditional Classification	ENETS/WHO Classification	Moran et al <sup>4</sup>
<b>Well differentiated</b>					
Low Grade (grade 1)	< 2	≤ 2	Carcinoid, islet cell, pancreatic (neuro) endocrine tumor	Neuroendocrine tumor, grade 1	Neuroendocrine carcinoma, grade 1
Intermediate Grade (grade 2)	2-20	3-20	Carcinoid, atypical carcinoid, ‡ islet cell, pancreatic (neuro) endocrine tumor	Neuroendocrine tumor, grade 2	Neuroendocrine carcinoma, grade 2
<b>Poorly differentiated</b>					
High Grade (grade 3)	> 20	> 20	Small-cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell	Neuroendocrine carcinoma, grade 3, small cell
			Large-cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell	Neuroendocrine carcinoma, grade 3, large cell
Abbreviations: ENETS, European Neuroendocrine Tumor Society. WHO, World Health Organization *Mitotic Count is per 10 high-power field = 2mm <sup>2</sup> ; at least 40 fields (at x40 magnification) were evaluated in areas of highest mitotic density. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition). <sup>3</sup> †MIB1 antibody; percentage of 2,000 tumor cells in areas of highest nuclear labeling. Cutoff values were taken from American Joint Committee on Cancer staging system (seventh edition). <sup>3</sup> ‡The term atypical carcinoid only applies to intermediate-grade neuroendocrine tumor of the lung.					

A variety of classifications and nomenclature conventions have been used to describe this disease. The 2010 WHO classification categorized pancreatic NET into groups based on tumor histology, proliferative indices, and cell size and the categories are now aligned with

the other commonly used systems. As seen in Table 1, pancreatic NET can generally be separated into two main groups: well differentiated (grade 1 or grade 2) or poorly differentiated (grade 3). These entities demonstrate vastly different prognoses, and thus the treatment approaches and clinical trials for these groups are entirely distinct. The well-differentiated tumor is the disease under study for this submission.<sup>1,5</sup>

Prognosis also varies by extent of disease at diagnosis: a recent analysis of patients with pancreatic NET from SEER database for 1973-2004 reported that 14% of patients present with localized disease, 22% with regional involvement and 64% with distant metastases at the time of diagnosis and median survival (in months) for these three groups were 136, 77, and 24, respectively.<sup>6</sup>

Given their ability for amine precursor uptake and decarboxylation (APUD), the putative cells of origin for pancreatic NET have been referred to as APUD cells. These cells form clusters within the pancreatic parenchyma. Specific cell types (alpha, beta, delta, G, and PP) produce the hormones glucagon, insulin, somatostatin, gastrin, and pancreatic polypeptide, respectively. The mechanism of malignant transformation of these cells remains poorly understood; however, these tumors do occur as part of inherited predisposition syndromes, including multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau (VHL). MEN1 is an autosomal dominant condition caused by mutation in the MEN1 gene on chromosome 11q13 which encodes for a 610 amino acid protein, menin, a nuclear protein that is a putative inhibitor of transcription. MEN1 is associated with several tumor types, and approximately 75% of individuals with this syndrome develop NET of the pancreatic islet cells or duodenum. VHL is an autosomal dominant disorder caused by mutation in the VHL tumor suppressor gene. The VHL gene product forms stable complexes with elongin B, elongin C, cullin 2, and Rbx1 to regulate the protein degradation of hypoxia inducible factor-alpha (HIF- $\alpha$ ). When VHL protein function is absent, HIF- $\alpha$  accumulates and binds with constitutively present HIF- $\beta$  forming a transcriptional factor complex that results in unregulated expression of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF bind to their respective tyrosine kinase receptors on the surface of endothelial cells and vascular pericytes, resulting in cell migration, proliferation, and survival. Phenotypically, both VEGF and PDGF promote tumor angiogenesis that may contribute to the hypervascular histology.

Indeed, pancreatic NET and their associated stroma have been shown to overexpress VEGF, PDGF, as well as their receptors VEGFR and PDGFR.<sup>7</sup> The VEGF pathway may be important in promoting tumor growth and angiogenesis through direct effects on the tumor vasculature,<sup>8-10</sup> while the PDGF pathway may be important for supporting pericytes within the tumor stroma and thereby cooperate with VEGF in tumor neoangiogenesis. Expression of VEGF has been associated with relatively short disease-free survival and overall survival. Additionally, a recent study demonstrated that low KIT expression (assessed by immunohistochemistry) in pancreatic NET biopsies was associated with prolonged survival, suggesting that KIT may similarly be a disease-specific target for pancreatic NET.<sup>11</sup>

Pancreatic NET are highly vascular tumors.<sup>12</sup> Inhibition of the VEGF pathway may lead to decreased tumor growth and metastasis and potentially to tumor regression.<sup>9,13</sup> Together,

these data suggest that VEGFR, PDGFR, and KIT are rational molecular targets in pancreatic NET.

## 1.2. Pancreatic NET Epidemiology

In the United States, the overall incidence of pancreatic NET was estimated by using the SEER registry for 2000 to 2004.<sup>6</sup> The median age of diagnosis of pancreatic NET was 60 years (mean 59 years, SD 15; SEER data 1973-2004), and the age-adjusted annual incidence of pancreatic NET was 0.32 per 100,000. Incidence among males was 0.38 per 100,000 and incidence among females was 0.27 per 100,000. Although such data do not exist in the European patient population, the incidence is predicted to be similar. While the SEER database reported that pancreatic NET accounted for only 5-8% of all NET, institutional databases have described it as 22-28% of all NET.<sup>14, 15</sup> The epidemiologic data on pancreatic NET are limited and potentially represent underreported data due to the lack of validated, well-defined pathologic criteria, and varying nomenclature for these rare and heterogeneous tumors. The incidence of pancreatic NET is reported to be higher in autopsy reports indicating a lower clinical detection rate.

## 1.3. Treatment of Pancreatic NET

The treatment of pancreatic NET requires a multidisciplinary approach with the goal of prolonging survival or providing symptom control and, thus, improving the quality of life of these patients.

The treatment planning for pancreatic NET begins with the evaluation of extent of tumor, metastases (if any), and secretory profile. As discussed earlier, the presentation of pancreatic NET is highly variable depending upon whether the tumor is functioning or nonfunctioning. Patients with functioning pancreatic NET may present with symptoms related to the overproduction of certain hormones or physiologically active tumor products ranging from dyspepsia, diarrhea, weakness, dizziness, weight loss, weight gain, flushing, skin rashes, jaundice, abdominal pain or abdominal mass. Non-functioning tumors present with symptoms secondary to mechanical problems caused by the tumor bulk or metastases, such as, jaundice secondary to a large head of pancreas tumor. Other common symptoms include abdominal pain, weight loss, or nausea and vomiting. Management of symptom control is required in both functioning and non-functioning tumors. Common therapies include the use of somatostatin (SS) analogues, proton pump inhibitors, glucocorticoids, anti-diarrheals, etc.

Surgery is the treatment of choice in patients with limited disease that involves primary +/- regional lymph nodes. Enucleation or distal pancreatectomy rather than Whipple resection may be possible depending on tumor size and location. Surgery offers greatest potential for cure through resection of the primary tumor and all lymph node metastases.

While pancreatic NET are typically considered a group of indolent diseases, 86% of patients present with locally advanced or metastatic disease at the time of diagnosis.<sup>6</sup> This subset of patients with unresectable, locally advanced or metastatic disease and recent disease progression demonstrate poor prognosis with a survival of 1-3 years. The goal of therapy in these patients is to improve and maintain an optimal quality of life. The choice of treatment

depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumor.

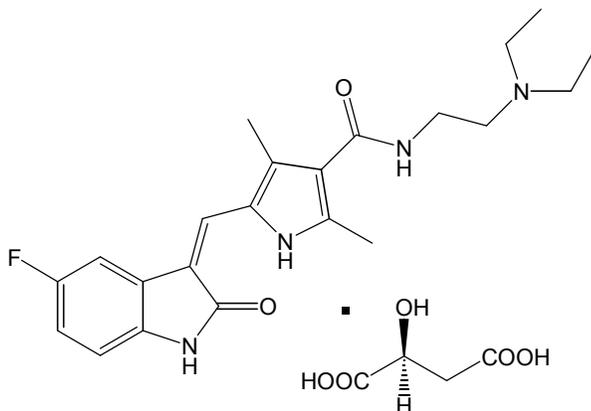
Treatment choices for unresectable disease include SS analogues, hepatic-directed therapy, or cytotoxic chemotherapy. Liver-directed therapies such as hepatic artery chemoembolization, radiofrequency ablation therapy, or ethanol injection are common as liver is the most frequent site of metastasis.<sup>16</sup> The benefit of these treatments in this disease has not been completely defined. SS analogues may be useful in ameliorating some hormonally related symptoms such as diarrhea; however, their antitumor efficacy has been limited primarily to low-volume midgut (but not pancreatic) tumors.<sup>17</sup> Trials of systemic chemotherapy have been conducted with agents including streptozocin, doxorubicin, and fluorouracil but have yielded low response rates and have been associated with adverse events that may outweigh any benefit.<sup>18-21</sup> Exploratory studies have also been conducted with newer agents, including temozolomide and thalidomide in Phase II trials, and with peptide receptor radionuclide therapy (PRRT).<sup>22, 23</sup> The potential benefits of streptozocin (even in combination with doxorubicin or 5-fluorouracil) and PRRT remain unclear. There remains considerable unmet medical need for an effective agent with an acceptable safety profile for the treatment of patients with pancreatic NET.

## 2. RATIONALE FOR DEVELOPING SUNITINIB FOR PANCREATIC NET

### 2.1. Pharmacologic Class

Sunitinib is a small molecule with the molecular formula C<sub>22</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>2</sub>. The free base has a molecular weight of 398.48, and the L-malate salt (Figure 1) has a molecular weight of 532.57. The chemical name of the L-malate salt is (Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (S)-2-hydroxysuccinate.

**Figure 1. Molecular Formula and Chemical Name**



Sunitinib malate drug substance has been identified by NMR spectroscopy as the (Z)-isomer.

## 2.2. Mechanism of Action

Sunitinib is an orally active small molecule with anti-tumor properties that are mediated through the inhibition of multiple receptor tyrosine kinases (RTKs). These RTKs are important in the regulation of tumor cell growth, pathologic angiogenesis, and metastasis. Specifically, sunitinib is a potent ATP-competitive inhibitor of the catalytic activity of a group of closely related RTKs consisting of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)- $\alpha$  and - $\beta$ , stem cell factor receptor (KIT), colony stimulating factor-1 receptor (CSF-1R), Fms-like tyrosine kinase-3 receptor (FLT-3), and glial cell line-derived neurotrophic factor receptor (rearranged during transfection, RET). VEGFR, PDGFR, and KIT are rational targets for the treatment of pancreatic NET. Sunitinib inhibits all 3 pathways, and hence, has potential for use in pancreatic NET.

## 2.3. Nonclinical Development Program

Nonclinical proof of concept for sunitinib in pancreatic islet cell carcinoma was first demonstrated in the RIP1-TAG2 transgenic mouse model, an *in vivo* mouse model of insulinoma developing *in situ*. The RIP1-TAG2 model comprises a strain of transgenic mice for which the rat insulin promoter (RIP) directs expression of the SV40 Large T antigen transgene (TAG) in beta cells of the pancreatic islets. The Large TAG oncogene is expressed beginning at embryonal day 8, and hyperplastic islets begin to appear by 3-4 weeks of age. Solid tumors consistently and reproducibly emerge initially as small encapsulated adenomas at about 10 weeks that progress into large adenomas by 12-13 weeks and to invasive cancer by 14 weeks.

Sunitinib was evaluated in both regression and regression/survival trials in the RIP1-TAG2 model. In regression or regression/survival trials, sunitinib was administered to 12-week-old RIP1-TAG2 mice bearing multiple large established adenomas. In these studies, sunitinib was associated with reduced tumor burden and stable disease over the 4-week administration cycle and with a significant survival advantage.<sup>24</sup> In longer term studies utilizing RIP1-TAG2 mice, administration of sunitinib starting at 12 weeks was markedly efficacious, producing a significant survival benefit and a 65% decrease in tumor burden after 5 weeks of treatment when compared to the age-matched control animals.<sup>25</sup> Mechanistic studies in the RIP1-TAG2 islet cell carcinoma model demonstrated that treatment with sunitinib for 7 days reduced both the endothelial cell population (69% reduction) and pericyte coverage (71% reduction) of tumor vessels,<sup>26</sup> consistent with the importance of inhibition of VEGF signaling pathways on blood vessels and PDGF signaling pathways on pericytes in islet cell tumors.

Thus, the putative role of sunitinib targets in this disease and the demonstration of efficacy in an elegant mouse model provided strong rationale for the evaluation of sunitinib in this disease setting.

### **3. SUNITINIB CLINICAL DEVELOPMENT PROGRAM AND REGULATORY HISTORY**

#### **3.1. Clinical Development Program**

Sunitinib has demonstrated efficacy in pivotal Phase III trials of metastatic renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST) confirming the critical role of VEGF and PDGF/KIT signaling pathways in these tumors, respectively. RCC are strongly associated with the VHL gene inactivation in  $\geq 90\%$  of cases. Phenotypically, RCC are highly vascular tumors with overexpression of VEGF, the pathway inhibited by sunitinib. More than 80% of GISTs express mutated, constitutively active KIT and another 5-7% GISTs express mutated PDGFRA; both KIT and PDGFR are inhibited by sunitinib. In 2006, Sunitinib was first approved in the United States (US) and Europe for the treatment of advanced RCC and for the treatment of GIST after disease progression on or intolerance to imatinib mesylate. Sunitinib has been approved for the treatment of RCC and GIST in more than 100 countries worldwide.

The VEGF, PDGF, and KIT signalling pathways are targets in pancreatic NET and all 3 pathways are inhibited by sunitinib. Thus, Phase II and III studies to evaluate the safety and efficacy of sunitinib in pancreatic NET were conducted. The use of sunitinib in pancreatic NET is supported by the results of a pivotal Phase III study (A6181111) and a supportive Phase II study (RTKC-0511-015). Two additional Phase II studies (A6181047 and A6181061) in GIST and RCC, respectively, support the continuous daily dosing (CDD) schedule used in the pivotal trial. On 11 December 2009, a type II variation including data to support a pancreatic NET indication was submitted to the European Medicines Agency (EMA). On 29 November 2010, the European Commission approved sunitinib for “the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with disease progression in adults. Experience with sunitinib as first-line treatment is limited.” Sunitinib has also been approved for the treatment of patients with pancreatic NET in Switzerland, Korea, the Philippines, Argentina, Colombia and Bolivia.

**Table 2. Sunitinib Studies**

<b>Protocol</b>	<b>Design and Objectives</b>	<b>N; Status</b>
<b>Pivotal Phase III Study</b>		
A6181111	Double-blind, randomized, controlled Phase III study to evaluate the efficacy and safety of sunitinib 37.5 mg (on Schedule CDD) versus placebo in patients with progressive advanced/metastatic well-differentiated pancreatic islet cell tumors	171; Stopped early due to positive efficacy
<b>Supportive Studies</b>		
<i>Studies in Subjects with Pancreatic Neuroendocrine Tumors</i>		
RTKC-0511-015	Open-label, randomized, multicenter, 2-cohort, Phase II study to investigate the efficacy and safety of single-agent sunitinib 50 mg (on Schedule 4/2) in subjects with unresectable neuroendocrine tumors; carcinoid tumors or pancreatic neuroendocrine tumors	66 (Pancreatic NET); 41 (Carcinoid); Completed
<b>Other Studies Evaluating Continuous Daily Dosing</b>		
A6181047	Open-label, uncontrolled, multicenter Phase II study to investigate the efficacy, safety/tolerability, and PK of sunitinib 37.5 mg (on Schedule CDD) in patients with advanced GIST	60; Completed
A6181061	Open-label, nonrandomized, multicenter Phase II study to investigate the efficacy, safety/tolerability, and pharmacokinetics of sunitinib 37.5 mg (on Schedule CDD) in patients with cytokine-refractory RCC	107; Completed

Abbreviations: CDD = continuous daily dosing; 4/2 = 4 weeks on treatment followed by 2 weeks off-treatment; GIST = gastrointestinal stromal tumor; RCC = renal cell carcinoma;; N = number of subjects  
Source: CSR Study A6181111; CSR Study RTKC-0511-015; CSR Study A6181047; CSR Study A6181061

### 3.2. Scientific Guidelines and Regulatory Agency Advice

The clinical development program supporting the proposed indication for the treatment of pancreatic NET has been planned, conducted, and analyzed in accordance with relevant guidance documents. The guidance for oncology drugs included the US FDA’s “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biological Products” (May 2007), “Cancer Drugs and Biological Products – Clinical Data in Marketing Applications” (October 2001), and the European Medicines Agency “Guidance on Evaluation of Anticancer Medicinal Product in Man” (June 2006, August 2008). All studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with the International Congress on Harmonization Good Clinical Practices Guidelines. Each investigational center obtained approval from their Institutional Review Board or Independent Ethics Committee. All subjects gave written informed consent before entering the trials. In addition, all local regulatory requirements were followed.

Specific guidance on the feasibility of submitting an application for the proposed indication for the treatment of pancreatic NET was received from Health Authorities including those in the US, EU, Canada and Japan.

Subsequent to the Sponsor’s acceptance of the DMC recommendation to stop the study early due to sunitinib benefit, a Type A meeting was held with the FDA on 18 May 2009 to discuss the preliminary results from the Phase III study (A6181111) and to seek the Agency’s advice on whether the proposed data package could support registration. The FDA agreed that the data package would support submission, noted that approvability would be a review issue, and recommended that a pre-sNDA meeting be requested to further discuss supplemental

New Drug Application (sNDA) requirements. Consequently, a Type B pre-sNDA meeting was held with the FDA on 16 September 2009, and agreement was reached on the proposed content and format of the sNDA.

### **3.3. Supplemental New Drug Application Submission**

A sNDA was submitted to the US FDA on 11 December 2009.

The pivotal study for the application was Study A6181111, a randomized, double-blind, placebo-controlled, Phase III study of sunitinib 37.5 mg administered on a CDD schedule in subjects with pancreatic NET, which included 83 subjects who received sunitinib and 82 subjects who received placebo. The data cutoff date for efficacy data in the original submission was 15 April 2009 and the data cutoff date for safety data was 13 May 2009. Included in the submission were 3 Phase II studies – a Phase II study in subjects with unresectable neuroendocrine tumors (RTKC-0511-015), and two Phase II studies of sunitinib in GIST (A6181047) and RCC (A6181061) on the CDD schedule (Table 2).

A 120-day safety update was submitted on 29 March 2010 to support the safety of sunitinib for the treatment of patients with pancreatic NET based on data from two ongoing, open-label (sunitinib) extension studies, Study A6181078 and Study A6181114. Safety data from subjects with pancreatic NET, who had previously participated in pivotal Study A6181111 (103 subjects evaluated for safety) were included in the Summary of Clinical Safety (SCS) Supplement. The safety data cutoff date for the SCS Supplement was 01 October 2009. Subjects from the placebo arm of Study A6181111 could have entered the extension studies upon documented evidence of disease progression. It should be noted that as a result of the early closure of Study A6181111 by the Sponsor, subjects from either the sunitinib or the placebo arm could have entered the extension studies at the time of that study closure.

At the request of US FDA, an updated analysis of the OS was provided with the 120-day safety update for subjects in pivotal Phase III sunitinib Study A6181111. The data cut-off date for updated OS information was 01 December 2009.

On 28 May 2010 the FDA issued a Complete Response (CR) letter requesting additional information in support of the sNDA, including a blinded independent central review (BICR), a recalculated PFS applying RECIST to all patients (algorithmic assessment), and a safety update. In December 2010 an amendment was submitted to the sNDA providing the information requested in the CR letter. Safety data were included in the amendment from the extension studies with a cutoff date of 01 June 2010.

## **4. SUNITINIB CLINICAL DEVELOPMENT PROGRAM IN UNRESECTABLE PANCREATIC NET**

### **4.1. Phase I Dose Escalating Study in Advanced Solid Tumors - RTKC-0511-002**

A dose finding Phase I study of sunitinib was conducted in 28 subjects with advanced solid tumors. The primary objective of this study was to assess the safety and tolerability of oral sunitinib by determining the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and the recommended dose for Phase II testing. Treatment consisted of escalating doses of

sunitinib during 28-day treatment cycles followed by 14 days off-treatment. The study established the recommended Phase II dose of sunitinib in advanced solid tumors as 30 mg/m<sup>2</sup> daily (equivalent to 50 mg daily for all subjects) with the primary DLT being asthenia/fatigue. Although this study was a dose finding Phase I study, observed anti-tumor activity included PRs in 2 of 4 subjects with neuroendocrine tumors. These results provided rationale for the Phase II study in pancreatic NET.

## **4.2. Phase II Supportive Study in Advanced Unresectable Pancreatic NET and Carcinoid Tumors - RTKC-0511-015**

### **4.2.1. Study Design**

Study RTKC-0511-015 was an open-label, single arm, non-randomized, multicenter, 2-stage, Phase II clinical trial that evaluated the activity and safety of single-agent sunitinib in subjects with advanced unresectable NET. Subjects with two forms of NET, carcinoid tumor and pancreatic islet cell tumors (also referred to as pancreatic NET in the WHO classification), were enrolled into separate cohorts. The primary objective of this study was to determine the antitumor activity of sunitinib administered at a starting dose of 50 mg orally once daily for 4 consecutive weeks followed by a 2-week off-treatment period repeated every 6 weeks (Schedule 4/2). Secondary objectives included the assessment of TTR, DR, TTP, and OS; the evaluation of the safety of sunitinib; and the evaluation of disease- and treatment-related symptoms assessed by the subjects, investigators, and laboratory tests.

#### **4.2.1.1. Subject Eligibility**

This study included subjects with histologically or cytologically proven diagnosis of carcinoid tumor or pancreatic islet cell tumors, not amenable to surgery, radiation, or combined modality therapy with curative intent. Subjects with small-cell carcinoma were excluded. Evidence of measurable disease per RECIST, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate vital organ function were also required for eligibility.

#### **4.2.1.2. Study Treatment**

Subjects received a starting dose of 50 mg sunitinib administered once daily on Schedule 4/2. The daily dose could be reduced to 37.5 mg and then to 25 mg in the event of toxicity. Also, the daily dose could be increased to 62.5 mg and then to 75 mg for subjects who tolerated the study medication.

#### **4.2.1.3. Efficacy Assessments**

##### **4.2.1.3.1. Primary and Secondary Endpoints**

The determination of antitumor activity was based on objective tumor assessments made according to RECIST. The preferred methods of tumor assessment were CT or MRI scans. The same method and technique was used for each subject throughout the study to

characterize each lesion that was identified and reported at baseline. ORR was the primary endpoint and the secondary endpoints included OS, DR, TTR and TTP.

**Objective Response Rate (ORR):** ORR was defined as the percent of subjects experiencing a confirmed CR or PR according to RECIST. Confirmed responses were those that persisted on repeat imaging  $\geq 4$  weeks after initial documentation of response.

**Overall Survival (OS):** OS was defined as the time from the first dose of study medication to the date of death due to any cause. In the absence of death, OS was censored at the last date the subject was known to be alive.

**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 PD or to death due to any cause. DR was calculated only for the subgroup of subjects with an OR.

**Time to Tumor Response (TTR):** TTR was defined as the time from the first study medication to the first documentation of objective tumor response (CR or PR) that was subsequently confirmed. The median TTR was calculated in the subgroup of subjects with an objective tumor response using Kaplan-Meier estimation.

**Time to Tumor Progression (TTP):** TTP was defined as the time from the date of first study medication to the date of PD.

#### 4.2.1.3.2. Other Parameters

**EQ-5D Questionnaire:** The EQ-5D Questionnaire was scored. At each assessment time point, summary statistics, including means, standard deviations, medians, minimums and maximums, of absolute scores and changes from baseline were calculated and tabulated.

**FACIT-Fatigue Scale:** The FACIT-Fatigue Scale was scored. Descriptive statistics, including means, standard deviations, medians, minimums and maximums, were calculated and tabulated for the raw scores and for changes from baseline by visit. Baseline was defined as the first assessment at Day 1 before the first dose of study drug.

**Tumor Markers:** Plasma chromogranin A (CgA) and other tumor markers (such as hormonal levels) were also collected for exploratory analysis.

#### 4.2.1.4. Safety Assessments

Safety evaluations included adverse events (from the first day of treatment to 28 days after the last dose of study drug), clinical laboratory tests, multigated acquisition (MUGA) scans to determine left ventricular ejection fraction (LVEF), electrocardiograms (ECGs), vital signs and ECOG performance status.

#### 4.2.1.5. Statistical Methods

##### 4.2.1.5.1. Sample Size

The sample size for each cohort was separately determined using Simon’s Minimax 2-stage design for Phase II studies. The null hypothesis was that the true ORR was  $\leq 5\%$ , and the alternative hypothesis was that the ORR resulting from treatment with sunitinib was  $\geq 15\%$ . Subjects with carcinoid tumor and pancreatic islet cell tumors were enrolled and evaluated separately. Initial enrollment into each cohort included 38 subjects, with the possibility of expansion to a total of 63 subjects in each cohort. If  $\leq 1$  subject among 38 subjects enrolled in a cohort experienced an objective tumor response, then the enrollment for that cohort was to be terminated, and the alternative hypothesis was to be rejected. However, if  $\geq 2$  subjects experienced an objective tumor response, then the cohort was to be expanded to enroll a total of 63 subjects (25 additional subjects enrolled). At the end of the study, if  $\geq 7$  subjects within a cohort experienced an objective tumor response, then the null hypothesis (that the true response probability was  $\leq 5\%$ ) was to be rejected.

##### 4.2.1.5.2. Analysis Population

**Intent-to-treat (ITT):** The ITT population included all subjects who enrolled in the study and received at least 1 dose of study medication. This population was the primary population for evaluating subject characteristics and all efficacy endpoints except DR and TTR, which were analyzed in the subset of responders.

#### 4.2.2. Subject Characteristics in Phase II Study RTKC-0511-015

##### 4.2.2.1. Subject Disposition in Pancreatic NET Cohort

Study RTKC-0511-015 included 107 subjects, of whom 66 had pancreatic NET. Of these 66 subjects, 21 (31.8%; Table 3) subjects completed the study and 45 (68.2%) subjects discontinued the study. The majority of discontinuations (28 subjects; 42.2%) were due to disease progression; other reasons for study discontinuation included adverse event (7 subjects; 10.6%), protocol violation (1 subject; 1.5%), and consent withdrawn (9 subjects; 13.6%). The median duration of follow-up was 12.5 months.

**Table 3. Subject Disposition in Pancreatic NET Cohort (ITT Population) - Study RTKC-0511-015**

Reason for Discontinuation	Pancreatic NET N = 66 n (%)
Adverse events	7 (10.6)
Protocol violation	1 (1.5)
Consent withdrawn	9 (13.6)
Lack of efficacy (disease progression)	28 (42.2)
Total Discontinued	45 (68.2)
Completed study	21 (31.8)

Abbreviations: ITT = intent to treat; N = number of subjects treated; n = number of subjects  
 Source: CSR Study RTKC-0511-015

#### **4.2.2.2. Demography, Baseline Characteristics, Disease Characteristics, and Prior Treatment in Pancreatic NET Cohort**

The median age of subjects in pancreatic NET cohort was 56 years (range 32-81; Table 4). A majority of subjects were male (42 subjects; 63.6%) and white (59; 89.4%). All subjects enrolled had an ECOG performance status of either 0 or 1. The median time from diagnosis was approximately 1.9 years. Approximately 70% of subjects had non-functioning tumors. Surgery was the most common prior therapy received by 98% of subjects. Prior use of systemic therapy was reported in 60.6% of subjects, while 16.7% of subjects had prior radiation therapy.

**Table 4. Demography, Baseline Characteristics, Disease Characteristics, and Prior Treatment in Pancreatic NET Cohort (ITT Population) - Study RTKC-0511-015**

<b>Demography</b>	<b>Pancreatic NET (N=66) Number (%) of subjects</b>
Age (years)	
Mean (SD)	54.2 (11.0)
Median (Range)	56 (32 – 81)
Age (n [%])	
<65 years	56 (84.8)
≥65 years	10 (15.2)
Sex (n [%])	
Male	42 (63.6)
Female	24 (36.4)
Race (n [%]) <sup>a</sup>	
White	59 (89.4)
Black	4 (6.1)
Asian	1 (1.5)
Other <sup>b</sup>	2 (3.0)
<b>Baseline Characteristics</b>	
ECOG performance status (n [%])	
0	36 (54.5)
1	30 (45.5)
2	0
<b>Disease Characteristics</b>	
Malignant neoplasm of islets of Langerhans[n (%)]	66 (100.0)
Median duration since first diagnosis (range) (weeks)	96.5 (1.9, 648.7)
Histological Classification - Non-Functioning	46 (69.7)
Histological Classification – Functioning	19 (28.8)
Gastrinoma	5 (7.6)
Glucagonoma	4 (6.1)
Insulinoma	3 (4.5)
VIPoma	2 (3.0)
Histological Classification - Other	5 (7.6)
Histological Classification – Unknown/missing	1 (1.5)
<b>Prior Treatment</b>	
Prior Surgeries [n (%)]	65 (98.1)
Prior radiation therapy [n (%)]	11 (16.7)
Prior systemic therapies	40 (60.6)

Abbreviations: N = total number of subjects included in the treatment population; n = number of subjects; NET = neuroendocrine tumors; SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat

<sup>a</sup>Local regulations prohibited some sites from recording race; for these sites, race was recorded as ‘other’

<sup>b</sup>Include those recorded as not applicable, refused, not allowed, not collected, unspecified, not listed, or other  
 Source: CSR Study RTKC-0511-015

#### 4.2.2.3. Exposure to Study Drug in Pancreatic NET Cohort

The median duration of treatment (defined as the number of days from first dose to 2 weeks after the last dose of study medication) was 213 days (range: 28 – 469; Table 5), and the median number of 6-week cycles started was 5 (range: 1 - 11). Forty-six (69.7%) subjects had at least 1 dosing interruption, and 34 (51.5%) subjects had a dose reduction. The median total dose delivered was 6231 mg (range: 850 to 13,300). Two (3%) subjects had dosing increased to 62.5 mg daily.

**Table 5. Exposure to Study Drug in Pancreatic NET Cohort (ITT Population) - Study RTKC-0511-015**

Variable	Pancreatic NET(N=66)
Number of cycles started	
Mean (SD)	5.3 (2.7)
Median (range)	5 (1 to 11)
Number of days on treatment <sup>a</sup>	
Mean (standard deviation)	219.2 (116.9)
Median (range)	213.5 (28 to 469)
Number of days on drug	
Mean (standard deviation)	137.8 (75.3)
Median (range)	138.5 (18 to 308)
Number (%) subjects with dosing interruptions	46 (69.7)
Number (%) subjects with dosing reductions	34 (51.5)
Reduction to 37.5 mg	33 (50)
Reduction to 25.0 mg	11 (16.7)
Number (%) subjects with dosing increase	2 (3.0)
Increase to 62.5 mg	2 (3.0)
Total dose administered (mg)	
Mean (standard deviation)	6132.2 (3298.4)
Median (range)	6231 (850 to 13,300)
Average daily dose (mg)	
Mean (standard deviation)	45.4 (6.3)
Median (range)	49.6 (28.3 – 58.3)
Relative dose intensity (%) <sup>b</sup>	
Mean (standard deviation)	91.0 (11.7)
Median (range)	94.4 (34.7 – 100.0)

Abbreviations: N = number of subjects; SD = standard deviation; ITT = intent to treat; mg = milligram

<sup>a</sup> Number of days from first dose to termination or 14 days after last dose

<sup>b</sup> Relative to assigned dose for each cycle, e.g., if a subject had a dose-reduction to 37.5 mg/day for Cycle 2, the subject can still be counted as having 100% dose intensity by completing 28 days at 37.5 mg.

Source: CSR Study RTKC-0511-015

#### 4.2.3. Efficacy Results in Pancreatic NET Cohort of Phase II Study RTKC-0511-015

##### 4.2.3.1. Primary and Secondary Endpoints

In the pancreatic NET cohort, 7 of the first 38 treated subjects had confirmed PRs (RECIST); therefore, enrollment was expanded to stage 2 and a total of 66 subjects were treated. With 11 PRs, the primary endpoint ORR was 16.7% (95% CI: 8.6 to 27.9; Table 6). The null hypothesis, that the true ORR was  $\leq 5\%$ , was rejected for this cohort; sunitinib treatment

resulted in a clinically meaningful ORR in subjects with pancreatic NET. Over 60% of the pancreatic NET subjects demonstrated some degree of tumor shrinkage as illustrated in Figure 2, and the majority of these subjects had stable disease (SD) by RECIST. Additionally, 45 (68.2%) subjects had SD on therapy; 37 (56.1%) subjects had SD for at least 6 months. Among 11 subjects who had a confirmed PR on sunitinib treatment, 10 subjects did not have documented disease progression, 8 of whom completed the study. The observed DRs were 1.4+, 1.7+, 2.8+, 2.8+, 2.9+, 4.7, 7.0+, 8.3+, 8.3+, 11.6+, and 12.5+ months.

The median TTR was 4.1 months (95% CI: 2.6 – 6.7 months). The median TTP from the Kaplan-Meier analysis was 7.8 months (95% CI: 6.6, 12.6) and the Kaplan-Meier analysis of TTP is shown in Figure 3.

While the median OS could not be estimated due to the limited number of events, the lower 95% CI of the median was estimated at 22.6 months (1.9 years). The Kaplan-Meier curve is presented in Figure 4.

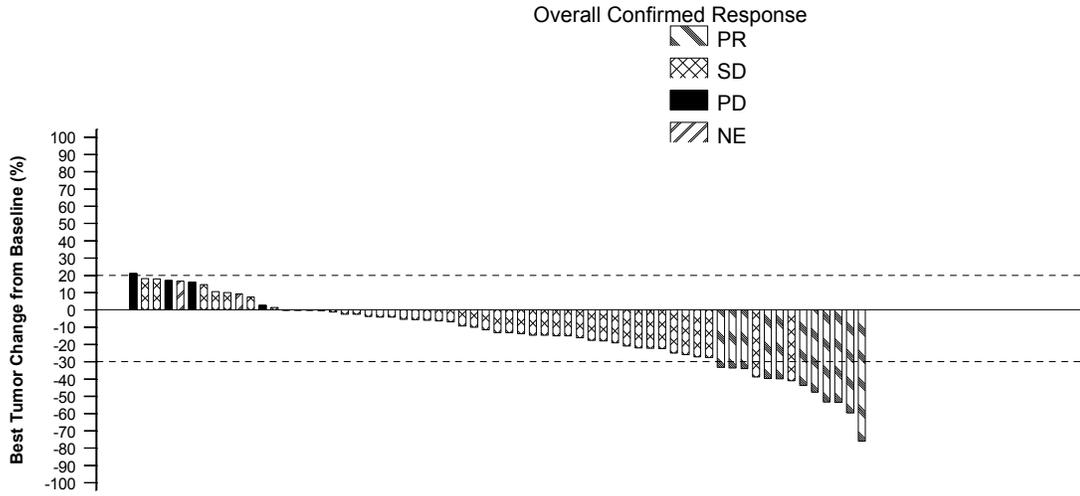
**Table 6. Efficacy Results in Pancreatic NET Cohort (ITT Population) - Study RTKC-0511-015**

Efficacy parameter	Pancreatic NET (N=66)
Best overall response	
CR [n (%)]	0
PR [n (%)]	11 (16.7)
SD [n (%)]	45 (68.2)
≥6 months	37 (56.1)
PD [n (%)]	5 (7.6)
ORR [(%) (95% CI)]	16.7 (8.6 – 27.9)
Secondary Endpoints [median (95% CI)] (months)	
TTR	4.1 (2.6 – 6.7)
DR [median (range)] (months)	NR (1.4+ – 12.5+)
TTP	7.8 (6.6 – 12.6)
OS	NR (22.6 – NC)

Abbreviations: N = number of subjects; CI = confidence interval; NET = neuroendocrine tumors; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; TTR = time to tumor response; DR = duration of response; TTP = time to tumor progression; OS = overall survival; NR = not reached; NC = not calculable.

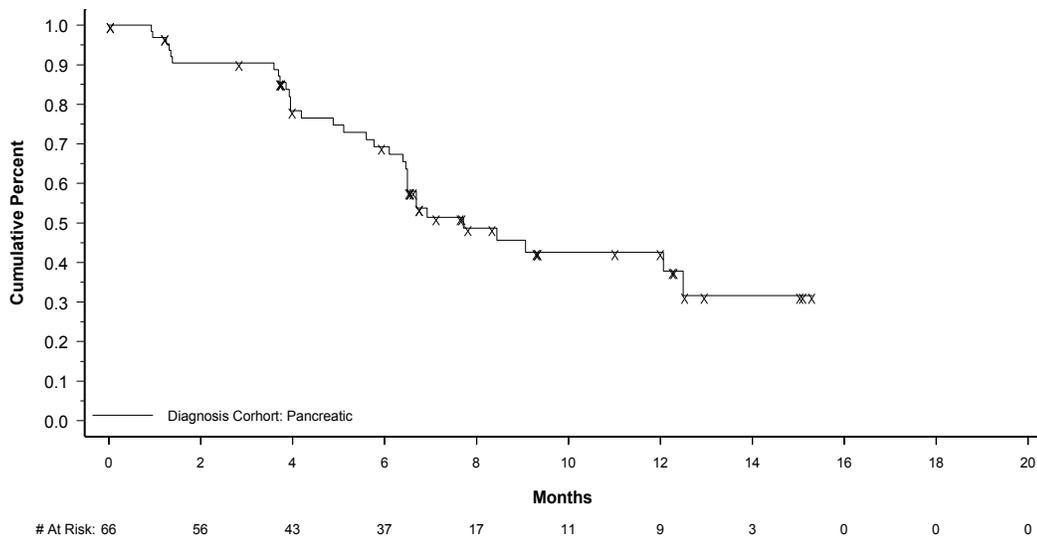
Source: CSR Study RTKC-0511-015

**Figure 2. Best Tumor Change-from-Baseline (%) for Target Lesions in Pancreatic NET Cohort (ITT Population) - Phase II Study RTKC-0511-015**



Abbreviations: PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.  
 Source: Summary of Clinical Efficacy

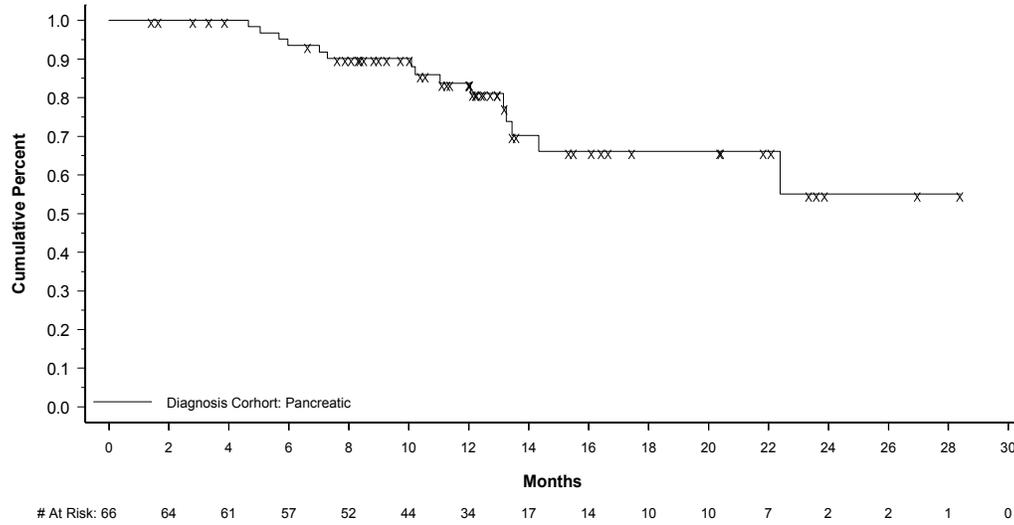
**Figure 3. Kaplan-Meier Curve of Time to Tumor Progression in Pancreatic NET Cohort (ITT Population) – Phase II Study RTKC-01511-015**



Source: Summary of Clinical Efficacy

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**Figure 4. Kaplan-Meier Curve of Overall Survival in Pancreatic NET Cohort (ITT Population) – Phase II Study RTKC-0511-015**



Source: Study RTKC-0511-015

#### 4.2.3.2. Other Parameters

There did not appear to be a meaningful change in EQ-5D results, though the FACIT-Fatigue scale findings suggested a small but reversible increase in patient-reported fatigue during treatment with sunitinib. Chromogranin A (CgA) and other tumor markers including hormonal levels were also collected for exploratory analysis. Twelve (57%) of 21 subjects with available tumor marker data (and elevation at baseline) demonstrated a tumor marker response, defined as at least a 50% reduction in one or more tumor marker levels from baseline to anytime on study.

#### 4.2.4. Efficacy Results in Carcinoid Tumor Cohort of Phase II Study RTKC-0511-015

Enrollment into the cohort of subjects with carcinoid tumor was discontinued at the end of the first stage of the study because the enrollment criteria for expansion were not met when only 1 (2.4%) of 41 subjects in the cohort had a confirmed response.

#### 4.2.5. Safety Results of Phase II Study RTKC-0511-015

##### 4.2.5.1. Treatment-Emergent, All-Causality Adverse Events

All 107 subjects experienced treatment-emergent, all-causality AEs. Adverse events were most commonly associated with the Gastrointestinal disorders SOC (100% of sunitinib subjects) or General disorders and administration site conditions SOC (96.3% of sunitinib subjects).

As summarized in Table 6, the most common treatment-emergent, all-causality AEs (reported in  $\geq 10\%$  of subjects in either the carcinoid tumor or pancreatic NET cohort) were consistent with conditions commonly associated with advanced pancreatic NET and with known toxicities of sunitinib. Common AEs were generally constitutional (fatigue, anorexia, headache, flushing, cough, pyrexia, and chills), gastrointestinal (diarrhea, nausea, abdominal pain, vomiting, glossodynia, stomatitis, constipation, dyspepsia, oral pain, and flatulence), cutaneous (rash, skin discoloration, hair color changes, and palmar-plantar erythrodysesthesia syndrome), or blood related (neutropenia, thrombocytopenia, and anemia); other common AEs were dysgeusia, myalgia, dyspnea, insomnia, pain in extremity, dizziness, arthralgia, paresthesia, edema peripheral, dehydration, back pain, hypertension, periorbital edema, and nasopharyngitis. The number and percent of subjects with grade 3/4 AEs are shown in Table 7.

**Table 7. Most Common ( $\geq 10\%$  Total Subjects) Treatment-Emergent, All-Causality Adverse Events by Cohort and by Maximum CTC Severity – Study RTKC-0511-015**

Preferred Term	Diagnosis Cohort			
	Carcinoid Tumor N=41		Pancreatic NET N=66	
	Number (%) of subjects			
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE	41 (100.0)	36 (87.8)	66 (100.0)	54 (81.8)
Fatigue	39 (95.1)	15 (36.6)	61 (92.4)	14 (21.2)
Diarrhea	38 (92.7)	4 (9.8)	52 (78.8)	3 (4.5)
Nausea	29 (70.7)	5 (12.2)	40 (60.6)	4 (6.1)
Dysgeusia	19 (46.3)	0 (0.0)	34 (51.5)	0 (0.0)
Abdominal Pain	23 (56.1)	5 (12.2)	29 (43.9)	8 (12.1)
Flushing	23 (56.1)	0 (0.0)	26 (39.4)	0 (0.0)
Anorexia	15 (36.6)	2 (4.9)	27 (40.9)	2 (3.0)
Headache	18 (43.9)	3 (7.3)	23 (34.8)	0 (0.0)
Vomiting	17 (41.5)	3 (7.3)	23 (34.8)	4 (6.1)
Myalgia	14 (34.1)	2 (4.9)	25 (37.9)	2 (3.0)
Rash	16 (39.0)	1 (2.4)	23 (34.8)	0 (0.0)
Skin discoloration	14 (34.1)	0 (0.0)	25 (37.9)	0 (0.0)
Glossodynia	13 (31.7)	3 (7.3)	23 (34.8)	0 (0.0)
Stomatitis	10 (24.4)	0 (0.0)	26 (39.4)	2 (3.0)
Constipation	14 (34.1)	0 (0.0)	21 (31.8)	0 (0.0)
Hair color changes	18 (43.9)	0 (0.0)	16 (24.2)	0 (0.0)
Dyspnea	12 (29.3)	2 (4.9)	20 (30.3)	2 (3.0)
Insomnia	10 (24.4)	0 (0.0)	21 (31.8)	2 (3.0)
Dyspepsia	10 (24.4)	0 (0.0)	18 (27.3)	1 (1.5)
Pain in extremity	8 (19.5)	1 (2.4)	19 (28.8)	1 (1.5)
Dizziness	13 (31.7)	0 (0.0)	14 (21.2)	0 (0.0)
Neutropenia	8 (19.5)	7 (17.1)	18 (27.3)	15 (22.7)
Thrombocytopenia	7 (17.1)	1 (2.4)	19 (28.8)	10 (15.2)
Oral pain	11 (26.8)	0 (0.0)	15 (22.7)	0 (0.0)
Arthralgia	10 (24.4)	0 (0.0)	16 (24.2)	1 (1.5)
Paresthesia	14 (34.1)	0 (0.0)	12 (18.2)	0 (0.0)
Edema peripheral	7 (17.1)	0 (0.0)	18 (27.3)	0 (0.0)
Pyrexia	8 (19.5)	0 (0.0)	17 (25.8)	2 (3.0)
Cough	11 (26.8)	0 (0.0)	13 (19.7)	0 (0.0)

**Table 7. Most Common (≥10% Total Subjects) Treatment-Emergent, All-Causality Adverse Events by Cohort and by Maximum CTC Severity – Study RTKC-0511-015**

Preferred Term	Diagnosis Cohort			
	Carcinoid Tumor N=41		Pancreatic NET N=66	
	Number (%) of subjects			
	All Grades	Grade 3/4	All Grades	Grade 3/4
Dehydration	10 (24.4)	4 (9.8)	13 (19.7)	5 (7.6)
Anemia	7 (17.1)	0 (0.0)	16 (24.2)	1 (1.5)
Back pain	9 (22.0)	2 (4.9)	13 (19.7)	1 (1.5)
Hypertension	6 (14.6)	3 (7.3)	16 (24.2)	9 (13.6)
Flatulence	10 (24.4)	0 (0.0)	12 (18.2)	0 (0.0)
Periorbital edema	11 (26.8)	0 (0.0)	8 (12.1)	0 (0.0)
Nasopharyngitis	11 (26.8)	0 (0.0)	8 (12.1)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	6 (14.6)	0 (0.0)	12 (18.2)	2 (3.0)
Chills	3 (7.3)	0 (0.0)	13 (19.7)	0 (0.0)
Neutrophil count decreased	6 (14.6)	3 (7.3)	9 (13.6)	6 (9.1)
Upper respiratory tract infection	5 (12.2)	0 (0.0)	10 (15.2)	0 (0.0)
Pharyngolaryngeal pain	6 (14.6)	0 (0.0)	9 (13.6)	0 (0.0)
Muscle spasms	6 (14.6)	0 (0.0)	8 (12.1)	0 (0.0)
Abdominal distension	7 (17.1)	0 (0.0)	7 (10.6)	0 (0.0)
Chest pain	6 (14.6)	1 (2.4)	7 (10.6)	2 (3.0)
Depression	5 (12.2)	0 (0.0)	8 (12.1)	1 (1.5)
Mucosal inflammation	7 (17.1)	3 (7.3)	5 (7.6)	0 (0.0)
Leukopenia	1 (2.4)	1 (2.4)	11 (16.7)	1 (1.5)
Epistaxis	5 (12.2)	0 (0.0)	7 (10.6)	0 (0.0)
Platelet count decreased	8 (19.5)	2 (4.9)	3 (4.5)	0 (0.0)
Anxiety	5 (12.2)	0 (0.0)	6 (9.1)	2 (3.0)
Hyperhidrosis	5 (12.2)	0 (0.0)	6 (9.1)	0 (0.0)
Oedema	3 (7.3)	0 (0.0)	8 (12.1)	0 (0.0)

Abbreviation: N = number of subjects

Source: CSR Study RTKC-0511-015

Overall, treatment-emergent, all-causality grade 3/4 AEs were experienced by 36 (87.8%) subjects in the carcinoid tumor cohort and 54 (81.8%) subjects in the pancreatic NET cohort. The most frequent grade 3/4 AEs (reported in ≥10% of subjects) were fatigue, neutropenia, abdominal pain, and nausea in the carcinoid tumor cohort. The most frequently reported grade 3/4 AEs in the pancreatic NET cohort were neutropenia, fatigue, thrombocytopenia, hypertension, and abdominal pain.

CTC v.2.0 did not include grade 5; Deaths are discussed in Section 4.2.5.3.

Blood pressure measurements relevant to hypertension are discussed in Section 4.2.5.6.

#### 4.2.5.2. Treatment-Related Adverse Events

All subjects except one (106/107) experienced an AE considered by the investigator to be related to sunitinib treatment. As with treatment-emergent, all-causality AEs, the most common treatment-related AEs (reported in ≥10% subjects) were consistent with common

conditions associated with advanced pancreatic NET and with known toxicities of sunitinib (Table 8).

**Table 8. Most Common (≥10% Total Subjects) Treatment-Related Adverse Events by Cohort and Maximum CTC Severity – Study RTKC-0511-015**

Preferred Term	Diagnosis Cohort			
	Carcinoid Tumor (N=41)		Pancreatic NET (N=66)	
	Number (%) of subjects			
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE	40 (97.6)	31 (75.6)	66 (100.0)	43 (65.2)
Fatigue	36 (87.8)	14 (34.1)	59 (89.4)	12 (18.2)
Diarrhea	27 (65.9)	2 (4.9)	43 (65.2)	3 (4.5)
Nausea	24 (58.5)	3 (7.3)	33 (50.0)	3 (4.5)
Dysgeusia	19 (46.3)	0 (0.0)	33 (50.0)	0 (0.0)
Skin discoloration	14 (34.1)	0 (0.0)	25 (37.9)	0 (0.0)
Glossodynia	13 (31.7)	3 (7.3)	23 (34.8)	0 (0.0)
Myalgia	13 (31.7)	1 (2.4)	22 (33.3)	1 (1.5)
Stomatitis	10 (24.4)	0 (0.0)	24 (36.4)	2 (3.0)
Hair color changes	18 (43.9)	0 (0.0)	16 (24.2)	0 (0.0)
Vomiting	13 (31.7)	3 (7.3)	19 (28.8)	4 (6.1)
Anorexia	9 (22.0)	1 (2.4)	21 (31.8)	2 (3.0)
Rash	11 (26.8)	1 (2.4)	17 (25.8)	0 (0.0)
Oral pain	11 (26.8)	0 (0.0)	15 (22.7)	0 (0.0)
Neutropenia	8 (19.5)	7 (17.1)	17 (25.8)	14 (21.2)
Thrombocytopenia	7 (17.1)	1 (2.4)	18 (27.3)	9 (13.6)
Headache	11 (26.8)	1 (2.4)	14 (21.2)	0 (0.0)
Flushing	10 (24.4)	0 (0.0)	11 (16.7)	0 (0.0)
Anemia	6 (14.6)	0 (0.0)	14 (21.2)	0 (0.0)
Dyspepsia	7 (17.1)	0 (0.0)	13 (19.7)	0 (0.0)
Paresthesia	10 (24.4)	0 (0.0)	9 (13.6)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	6 (14.6)	0 (0.0)	12 (18.2)	2 (3.0)
Hypertension	4 (9.8)	3 (7.3)	13 (19.7)	8 (12.1)
Periorbital edema	11 (26.8)	0 (0.0)	6 (9.1)	0 (0.0)
Dehydration	5 (12.2)	2 (4.9)	11 (16.7)	3 (4.5)
Pain in extremity	4 (9.8)	1 (2.4)	11 (16.7)	0 (0.0)
Arthralgia	4 (9.8)	0 (0.0)	11 (16.7)	1 (1.5)
Dizziness	8 (19.5)	0 (0.0)	7 (10.6)	0 (0.0)
Neutrophil count decreased	5 (12.2)	3 (7.3)	9 (13.6)	6 (9.1)
Leukopenia	1 (2.4)	1 (2.4)	11 (16.7)	1 (1.5)
Mucosal inflammation	6 (14.6)	3 (7.3)	5 (7.6)	0 (0.0)
Platelet count decreased	8 (19.5)	2 (4.9)	3 (4.5)	0 (0.0)
Insomnia	2 (4.9)	0 (0.0)	9 (13.6)	0 (0.0)

Abbreviation: N = number of subjects  
Source: CSR Study RTKC-0511-015

Overall, most treatment-related AEs were grade 1 or 2 in severity. Grade 3/4 treatment-related AEs were experienced by 31 (75.6%) subjects in the carcinoid tumor cohort and 43 (65.2%) subjects in the pancreatic NET cohort. The most frequent (reported in ≥10% of subjects) grade 3/4 treatment-related AEs were fatigue and neutropenia in the carcinoid tumor cohort and fatigue, neutropenia, thrombocytopenia, and hypertension in the pancreatic NET cohort.

Due to the use of CTC v.2.0 in this study, fatal AEs were reported as grade 4 in severity. On-study deaths are discussed in Section 4.2.5.3 and blood pressure measurements relevant to hypertension are discussed in Section 4.2.5.6.

#### 4.2.5.3. Deaths

A total of 27 subjects died during the study. Four (6.1%) subjects in the pancreatic NET cohort and 2 (4.9%) in the carcinoid cohort died while on study. Five (83.3%) on-study deaths were considered to be due to progression of the underlying cancer; 1 on-study death was attributed to treatment with sunitinib: Subject 015-115396-0092 died as the result of a gastrointestinal hemorrhage. A summary of this case is provided below.

Subject 015-115396-0092, a 57-year-old white female, died of a GI hemorrhage on (b) (6) (b) (6) which was 4 days after her last dose of sunitinib. Sunitinib was administered on Schedule 4/2 from (b) (6), a total of 217 days (50 mg sunitinib daily in cycle 1, 37.5 mg sunitinib daily in cycles 2-4, and 25 mg sunitinib for 1 day during cycle 2). Concomitant medications taken within 2 weeks prior to and during the event included acetylsalicylic acid; Boost (nutritional beverage); darbepoetin alfa; diphenhydramine hydrochloride, lorazepam; furosemide, hydrochlorothiazide/olmesartan, spironolactone; ibuprofen and oxycodone; insulin glargine, insulin lispro; pantoprazole, lansoprazole, sucralfate; tegaserod; and Vicodin (hydrocodone/acetaminophen). The subject was initially diagnosed with pancreatic islet cell cancer on 26 Sep 2003. At screening, she presented with the primary tumor and lesions in the mesenteric lymph nodes, and malignant ascites. Previous systemic therapies included cisplatin and irinotecan from 28 Oct 2003 through 02 Apr 2004. Previous anti-cancer surgery included exploratory laparotomy, biopsy of peritoneal implant, and biopsy of mesenteric lymph node on (b) (6). At study entry, the subject was experiencing diabetes and hypertension. She had a history of abdominal discomfort and constipation. The subject was admitted to the hospital on (b) (6) (Study day 19; cycle 4, day 30) with a GI bleed associated with hemorrhagic shock. The platelet count was 90 X 10<sup>3</sup>/UL at cycle 4, Day 28. The GI hemorrhage was assessed as a grade 4 SAE on this same day. She underwent an emergency celiac and superior mesenteric artery arteriogram, which failed to embolize the bleeding. The gastroduodenal artery was embolized, although the physician did not feel that this was the source of her ongoing hemorrhage. On the same day, a repeat esophagogastroduodenoscopy showed a large clot in the entire stomach with no options for local therapy. The subject continued to have unremitting GI hemorrhage associated with respiratory and renal failure (no laboratory values provided). The subject also experienced hematemesis, which was assessed as not related to study drug and she recovered from hematemesis on 05 Feb 2005. She expired from GI hemorrhage on (b) (6). An autopsy was not performed. Sunitinib was permanently discontinued in response to this SAE with the last dose given on (b) (6).

Twenty-one (19.6%) subjects died during the follow-up period. Most deaths reported during the follow-up period were attributed to disease progression; there were no deaths attributed to treatment with sunitinib.

#### **4.2.5.4. Other Serious Adverse Events**

##### **4.2.5.4.1. Frequency of Treatment-Emergent All-Causality Serious Adverse Events**

Thirty-nine (16%) subjects in the carcinoid tumor cohort and 23 (34.8%) subjects in the pancreatic NET cohort experienced at least 1 treatment-emergent, all-causality SAE; SAEs were most commonly reported for the Gastrointestinal Disorders SOC. The most common treatment-emergent, all-causality SAEs for sunitinib-treated subjects (experienced by at least 2% of the subjects in either cohort) are summarized in Table 9. Events reported in  $\geq 2$  (3.0%) subjects with Pancreatic NET were dehydration and vomiting (5 subjects each, 7.6%), nausea (4 subjects, 6.1%), abdominal pain and fatigue (3 subjects each, 4.5%), and hypertension, hyponatraemia, chest pain, pneumonia, and dyspnea (2 subjects each, 3.0%).

**Table 9. Most Common (≥2% Sunitinib-Treated Subjects)  
Treatment-Emergent, All-Causality Serious Adverse Events  
by Cohort – Study RTKC-0511-015**

Preferred Term	Diagnosis Cohort Number (%) of subjects	
	Carcinoid Tumor (N=41)	Pancreatic NET (N=66)
Any serious adverse event	16 (39.0)	23 (34.8)
Abdominal Pain	4 (9.8)	3 (4.5)
Dehydration	2 (4.9)	5 (7.6)
Vomiting	0 (0.0)	5 (7.6)
Fatigue	2 (4.9)	3 (4.5)
Nausea	0 (0.0)	4 (6.1)
Hypertension	2 (4.9)	2 (3.0)
Hyponatremia	1 (2.4)	2 (3.0)
Chest pain	1 (2.4)	2 (3.0)
Pulmonary embolism	2 (4.9)	1 (1.5)
Hypotension	2 (4.9)	1 (1.5)
Neutropenia	1 (2.4)	1 (1.5)
Thrombocytopenia	2 (4.9)	0 (0.0)
Diarrhea	1 (2.4)	1 (1.5)
Gastrointestinal hemorrhage	1 (2.4)	1 (1.5)
Glossodynia	2 (4.9)	0 (0.0)
Small intestinal obstruction	1 (2.4)	1 (1.5)
Pyrexia	1 (2.4)	1 (1.5)
Pneumonia	0 (0.0)	2 (3.0)
Mental status changes	2 (4.9)	0 (0.0)
Dyspnea	0 (0.0)	2 (3.0)
Tachycardia	1 (2.4)	0 (0.0)
Abdominal discomfort	1 (2.4)	0 (0.0)
Melena	1 (2.4)	0 (0.0)
Peritoneal hemorrhage	1 (2.4)	0 (0.0)
Disease progression	1 (2.4)	0 (0.0)
Peritonitis	1 (2.4)	0 (0.0)
Sinusitis	1 (2.4)	0 (0.0)
Lipase increased	1 (2.4)	0 (0.0)
Hypocalcaemia	1 (2.4)	0 (0.0)
Syncope	1 (2.4)	0 (0.0)
Confusional state	1 (2.4)	0 (0.0)
Benign prostatic hyperplasia	1 (2.4)	0 (0.0)
Orthostatic hypotension	1 (2.4)	0 (0.0)

Abbreviation: N = number of subjects

Source: CSR Study RTKC-0511-015

#### 4.2.5.5. Other Significant Adverse Events

##### 4.2.5.5.1. Adverse Events Associated with Permanent Discontinuation

Twelve (11.2%) subjects, including 4 (9.8%) subjects in the carcinoid tumor cohort and 8 subjects (12.1%) in the pancreatic NET cohort, experienced a total of 21 AEs that led to their discontinuation from the study. Five (4.7%) subjects discontinued due to occurrence of 5

AEs related to the study drug. These 5 AEs were fatal gastrointestinal hemorrhage (Subject 015-115396-0092; in the pancreatic NET cohort), grade 3 mucosal inflammation (Subject 015-048461-0028; in the carcinoid tumor cohort; subject had 4 other events: atrial fibrillation, gastrointestinal hemorrhage, melena, and hypotension), grade 3 nausea (Subject 015-043641-0003; in the pancreatic NET cohort), grade 3 transaminases increased (Subject 015-113574-0098; in the pancreatic NET cohort), and grade 2 ejection fraction decreased (Subject 015-115396-0018; in the pancreatic NET cohort).

Four (3.7%) subjects discontinued because of AEs related to the underlying cancer and not due to treatment with sunitinib; these events were grade 4 disease progression, grade 4 pulmonary embolism, and grade 1 confusion and dyspnea (Subject 015-046059-0020), grade 3 small intestinal obstruction (Subject 015-038868-0106), grade 3 mental status changes (Subject 015-043641-0011), and grade 3 lipase increased (Subject 015-115396-0072).

Three (2.8%) subjects discontinued for AEs neither related to study drug nor disease progression; the events for these subjects were grade 4 pulmonary embolism and grade 3 peritoneal hemorrhage and hypocalcaemia (Subject 015-043641-0039), grade 3 hypothyroidism (Subject 015-045063-0062), and grade 2 blood creatinine increased (Subject 015-038868-0094).

#### **4.2.5.5.2. Adverse Events Associated with Temporary Discontinuations or Dose Reductions**

Overall, 73 (68.2%) subjects, 28 (68.3%) subjects in the carcinoid tumor cohort and 45 (68.2%) subjects in the pancreatic NET cohort experienced a delay or change in dosing because of AEs at some time during the study. Adverse events that most commonly led to dose reductions or delays included Gastrointestinal disorders [35 subjects; 32.7% including vomiting (13 subjects), nausea (12 subjects), and glossodynia (6 subjects)], General disorders and administration site conditions [27 subjects; 25.2% including fatigue (18 subjects)], Investigations [19 subjects; 17.8% including neutrophil count decreased (8 subjects)], Blood and lymphatic system disorders [16 subjects; 15.0% including thrombocytopenia (8 subjects) and neutropenia (8 subjects)], Metabolism and nutrition disorders [11 subjects; 10.3% including dehydration (9 subjects)], Vascular disorders [10 subjects; 9.3% including hypertension (9 subjects)], and Infections and infestations (8 subjects; 7.5%).

#### **4.2.5.6. Analysis of Adverse Events by Organ System or Syndrome**

##### **4.2.5.6.1. Cardiac Dysfunction**

Measurements of cardiac function were performed in Study RTKC-0511-015 at protocol-specified time points during the study. AEs indicative of cardiac dysfunction (e.g., preferred terms [PTs] in the Cardiac Disorders SOC such as cardiac failure, cardiomyopathy, congestive heart failure, ventricular failure/dysfunction, and ejection fraction decreased) are reported in this section.

One subject (Subject 015-038868-0106, a 60-year-old white male in the pancreatic NET cohort) experienced grade 4 congestive cardiac failure which began on cycle 1, day 38 and resolved 11 days later. This event was considered related to study treatment. The subject

had experienced a cerebrovascular accident 3 days prior to the cardiac failure, and he had discontinued the study 1 day later because of an AE (small intestinal obstruction).

Three subjects in the pancreatic NET cohort experienced grade 2 ventricular dysfunction considered to be related to study treatment.

One subject in the pancreatic NET cohort experienced grade 1 AE with the PT cardiac disorder considered not to be related to study treatment.

Nine (8.4%) subjects, 1 (2.4%) subject in the carcinoid tumor cohort and 8 (12.1%) subjects in the pancreatic NET cohort, experienced AEs of ejection fraction decrease. All 9 events were considered to be related to study treatment. Of these, 6 had a maximum intensity of grade 1, and 3 had a maximum intensity of grade 2. However, based on MUGA scans, there was no evidence of a clinically significant mean decrease in LVEF during treatment. Two subjects (1.9%) in the pancreatic NET cohort experienced a decrease from baseline of at least 20 percentage points to below the lower limit of normal (LLN) according to the LVEF data. No subjects experienced LVEF  $\leq$ 40% in this study.

#### **4.2.5.6.2. Thyroid Dysfunction**

No subjects experienced hyperthyroidism, while 2 subjects experienced hypothyroidism. One subject in the pancreatic NET cohort experienced grade 1 hypothyroidism that was considered to be related to study treatment. The subject remained on treatment, and the event increased in severity to grade 2 on cycle 3, day 29, and the event resolved 13 days later. On cycle 7, day 35, the subject experienced grade 3 hypothyroidism. This last event was considered unrelated to study treatment, but the subject discontinued the study because of it. One subject in the carcinoid tumor cohort experienced grade 2 hypothyroidism considered related to study treatment.

Thyroiditis was reported for 1 subject in the pancreatic NET cohort and no subjects in the carcinoid tumor cohort. This event was grade 2 in severity and considered unrelated to study treatment.

Blood TSH increased was reported as an AE for 1 subject in the carcinoid tumor cohort and no subjects in the pancreatic NET cohort. This event was grade 1 in severity and considered unrelated to study treatment.

No cases of grade 4 or fatal thyroid dysfunction were reported as an AE in this study.

#### **4.2.5.6.3. Hemorrhagic Events**

Of 5 subjects who experienced grade 3 or 4 bleeding events, 2 had treatment-related grade 3 or 4 bleeding events.

Subject 015-113574-0078, a 55-year-old white male in the pancreatic NET cohort, experienced grade 4 lower gastrointestinal hemorrhage beginning on day 23 of cycle 1. This event was considered related to the study drug. The event resolved after 3 weeks, and the

sunitinib dose was reduced to 37.5 mg daily. The subject remained on study for a total of 5 cycles of treatment, and the event did not recur.

Subject 015-115396-0092, a 57-year-old white female in the pancreatic NET cohort, experienced grade 4 gastrointestinal hemorrhage beginning on day 30 of cycle 4. This event was considered related to the study drug. The subject died as a result of the event.

Grade 3 or 4 bleeding events not considered related to study treatment were grade 4 melena (Subject 015-048461-0028) and grade 3 peritoneal hemorrhage (Subject 015-043641-0039), rectal hemorrhage (Subject 015-045063-0083), and hematemesis (Subject 015-115396-0092).

Twelve (11.2%) subjects experienced epistaxis; all cases were grade 1 or 2 in severity, and most were considered related to study treatment.

#### **4.2.5.6.4. Thromboembolic Events**

Three subjects experienced a total of 3 AEs of pulmonary embolism, 2 of which were considered related to sunitinib treatment. No subjects experienced deep vein thrombosis, or vena cava thrombosis. One subject experienced grade 4 cerebrovascular accident.

Subject 015-043641-0039, a 69-year-old white male in the carcinoid tumor cohort, experienced grade 4 pulmonary embolism beginning on cycle 1, day 47. This event was considered unrelated to the study drug. The subject discontinued the study because of the AE, and the event resolved the following day.

Subject 015-046059-0020, a 57-year-old white male in the carcinoid tumor cohort, experienced grade 4 pulmonary embolism beginning on cycle 1, day 13. This event was considered unrelated to the study drug. The subject discontinued the study because of the AE, and the outcome of the event was unknown.

Subject 015-046059-0029, a 54-year-old white male in the pancreatic tumor cohort, experienced grade 4 pulmonary embolism beginning on cycle 3, day 39. This event was considered related to the study drug. The subject remained on treatment but discontinued the study because of lack of efficacy (disease progression) during cycle 4. The subject died (disease-related respiratory failure), and the pulmonary embolism was ongoing until death.

Subject 015-038868-0106, a 60-year-old white male in the pancreatic tumor cohort, experienced grade 4 cerebrovascular accident beginning on day 35 of cycle 1. This event was considered related to the study drug. Two days later, grade 3 thrombocytopenia was reported. The cerebrovascular accident resolved after 2 weeks, by which time the thrombocytopenia had also resolved. The subject had discontinued the study after cycle 1 because of disease-related small intestinal obstruction.

#### **4.2.5.6.5. Hypoglycemia**

Three (4.5%) subjects in the pancreatic NET cohort experienced AEs of hypoglycemia. There was 1 event each of grade 1, grade 2, and grade 3 severity; none of these events was considered related to study treatment.

#### **4.2.5.7. Clinical Laboratory Evaluations**

Of the clinical laboratory data summarized in the following section, abnormal values that the investigator determined to be clinically significant were reported as AEs.

Subjects, who had abnormal hematology, chemistry, or coagulation test results of grade 3/4, are summarized in Table 10. ANC and lymphocytes were the most commonly reported hematology test result abnormalities of grade 3 maximum severity in both cohorts, and ANC was the only reported laboratory abnormality of grade 4 severity in both cohorts. Lipase was the most commonly reported chemistry test abnormality of grade 3 maximum severity in both cohorts, and uric acid was the most commonly reported chemistry test abnormality of grade 4 maximum severity in both cohorts. Only 1 subject had a coagulation test result of maximum severity grade 3 or greater.

**Table 10. Summary of Subjects with Grade 3 or 4 Chemistry Abnormalities (All Cycles) – Study RTKC-0511-015**

	Diagnosis Cohort			
	Number (%) of Subjects			
	Carcinoid (N=41)		Pancreatic (N=66)	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Hematology</b>				
ANC	9 (22.0)	2 (4.9)	22 (33.3)	3 (4.5)
Hemoglobin	2 (4.9)	0 (0.0)	1 (1.5)	0 (0.0)
Lymphocytes	5 (12.2)	0 (0.0)	23 (34.8)	0 (0.0)
Platelets	3 (7.3)	0 (0.0)	6 (9.1)	0 (0.0)
WBC	3 (7.3)	0 (0.0)	12 (18.2)	0 (0.0)
<b>Chemistry</b>				
ALT	1 (2.4)	0 (0.0)	3 (4.5)	0 (0.0)
AST	1 (2.4)	0 (0.0)	3 (4.5)	0 (0.0)
Albumin	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Alkaline phosphatase	2 (4.9)	0 (0.0)	5 (7.6)	0 (0.0)
Amylase	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Indirect bilirubin	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Hypocalcemia	0 (0.0)	1 (2.4)	2 (3.0)	0 (0.0)
Creatine kinase	0 (0.0)	0 (0.0)	2 (3.0)	1 (1.5)
Hyperglycemia	2 (4.9)	0 (0.0)	9 (13.6)	0 (0.0)
Lipase	4 (9.8)	1 (2.4)	10 (15.2)	1 (1.5)
Hypophosphatemia	3 (7.3)	0 (0.0)	5 (7.6)	0 (0.0)
Hypokalemia	1 (2.4)	0 (0.0)	1 (1.5)	0 (0.0)
Hyponatremia	1 (2.4)	0 (0.0)	2 (3.0)	1 (1.5)
Total bilirubin	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)
Uric acid	0 (0.0)	6 (14.6)	0 (0.0)	3 (4.5)
<b>Coagulation</b>				
Prothrombin	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)

Source: CSR Study RTKC-0511-015

Although transient, asymptomatic hyperlipasemia and, less frequently, hyperamylasemia have been previously observed in some subjects receiving sunitinib, there was no evidence in this study of a mean increase from baseline in either lipase or amylase. Sixteen (15%) subjects had grade 3 or 4 lipase (including 3 subjects who had grade 3 or 4 lipase at baseline); 1 (0.9%) subject had grade 3 amylase on study (1 additional subject had grade 3 amylase at baseline that did not recur on study). Of the 16 subjects with grade 3 or 4 lipase, 3 had grade 3 lipase at baseline and repeatedly throughout the study. Of the 13 subjects with shifts from grade 2 or less to grade 3 or greater lipase, 7 had a single grade 3 lipase result, and all 7 had a grade 2 or lower result at the next assessment. Six subjects with grade 2 or lower lipase at baseline had more than 1 on-treatment result of grade 3 or greater. Five subjects had a normal result following the grade 3 result; all 5 remained on study. One subject discontinued the study with ongoing grade 4 lipase levels.

Ninety-two subjects (41 in the carcinoid tumor cohort and 51 in the pancreatic NET cohort) had baseline ACTH-stimulation tests, and 85 of these subjects had post-baseline ACTH-stimulation results available. Not all subjects were evaluated because the requirement for ACTH stimulation testing was eliminated by protocol amendment after review of data from

other trials indicated that the testing did not reveal clinically significant adrenal dysfunction related to sunitinib administration. Of the 85 subjects with post-baseline results, 79 had normal results at baseline, and 6 had abnormal results at baseline. Of the 79 subjects with normal results at baseline and post-baseline results available, 6 (7% subjects with normal results at baseline) had at least one abnormal result post-baseline. Of the 6 subjects with abnormal results at baseline and post-baseline results available, 2 had at least 1 abnormal result post-baseline, and 4 had normal results at all post-baseline observations. In addition, all subjects underwent adrenal gland imaging, the results of which showed no evidence of adrenal hemorrhage.

#### **4.2.5.8. Vital Signs and Electrocardiograms Related to Safety**

##### **4.2.5.8.1. Vital Signs**

Hypertension was defined as systolic blood pressure >150 and/or diastolic blood pressure >100 mmHg. Fifty-three (49.5%) subjects, 21 (52.1%) subjects in the carcinoid tumor cohort and 32 (48.5%) subjects in the pancreatic NET cohort experienced hypertension at least once during the study. Four of these subjects (3.7% overall; 2 in each tumor type cohort) experienced systolic blood pressure >200 mmHg and/or diastolic blood pressure >110 mmHg. Three of the 4 subjects were being treated for hypertension at the start of the study. One of the subjects experienced an AE of hypertension but recovered, and the event did not recur. No subjects discontinued the study because of an AE of hypertension.

##### **4.2.5.8.2. Electrocardiograms**

The mean QTc interval measured at cycle 2 was similar to the pre-treatment value. Most subjects (95/100) had QTc intervals <450 msec. One (0.9%) subject experienced grade 3/4 (>500 msec) prolongation of the QTc interval. Subject 015-043641-0068, a 59-year-old black male in the pancreatic NET cohort, had a QTc interval of 451 msec (grade 1) at baseline; the subject's medical history included hypertension, syncope, atrial fibrillation, and ECG abnormal. The subject underwent ECG assessment at day 28 of each cycle; the clinically significant abnormality was still present at cycle 1, day 28, but was not considered clinically significant at cycles 2, 3, and 4. On cycle 5, day 28, the subject's QTc interval was 594 msec (increase from baseline of 143 msec; grade 3/4). No AE was reported. The subject discontinued the study after cycle 5 because of lack of efficacy (progressive disease), and no further information on this abnormality was available.

#### **4.2.6. Summary of Phase II Study RTKC-0511-015**

Sunitinib treatment, at a starting dose of 50 mg daily for 4 consecutive weeks in repeated 6-week cycles, produced a clinically significant ORR of 16.7% (all PRs, 95% CI: 8.6 – 27.9) in subjects with advanced unresectable pancreatic islet cell tumors. Of note, 10 of 11 subjects with PRs did not have documented disease progression and 8 of these patients completed the study. The DR ranged from 1.4+ to 12.5+ months indicating durable responses. The median TTR was 4.1 months (95% CI: 2.6 – 6.7 months). The median TTP based on Kaplan-Meier analysis was 7.8 months (95% CI: 6.6 – 12.6), which further supports the antitumor activity of sunitinib in subjects with advanced unresectable pancreatic NET. The toxicity profile of

sunitinib at this schedule was generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy in this study. The AE profile of sunitinib was characterized by gastrointestinal, constitutional, cutaneous, and myelosuppressive events that were generally of mild to moderate severity and was consistent with the signs and symptoms of pancreatic NET and the known clinical toxicities of sunitinib. One death was attributed to sunitinib treatment. The results from the Phase II supportive study in pancreatic NET cohort suggest that sunitinib treatment at 50 mg daily for 4 consecutive weeks in repeated 6-week cycles is well tolerated with antitumor activity.

### **4.3. Pivotal Phase III Randomized, Double-Blind Study of Sunitinib vs. Placebo in Progressive Advanced/Metastatic Well-Differentiated Pancreatic Islet Cell Tumors - A6181111**

#### **4.3.1. Study Design**

Study A6181111 was a randomized, double-blind, placebo-controlled, Phase III trial of sunitinib vs. placebo in subjects with progressive advanced/metastatic well-differentiated pancreatic islet cell tumors. The primary objective of the study was to compare PFS in subjects treated with sunitinib with those treated with placebo. Secondary objectives were to compare the OS, ORR, DR, TTR, PROs, and safety in the sunitinib and placebo treatment arms.

##### **4.3.1.1. Subject Eligibility**

Key inclusion criteria were histologically or cytologically proven diagnosis of well-differentiated pancreatic islet cell tumor (according to WHO 2000 classification) locally-advanced or metastatic disease with disease progression documented radiographically (CT, MRI, or Octreoscan<sup>®</sup>) per RECIST within 12 months prior to randomization, disease not amenable to surgery, radiation, or combined modality therapy with curative intent, presence of at least one measurable target lesion according to RECIST, adequate organ function, ECOG performance status 0 or 1, and life expectancy  $\geq$  3 months.

Subjects were excluded from the study if they had poorly differentiated pancreatic NET, were on current treatment for the disease other than somatostatin analogs, had prior treatment with any tyrosine kinase inhibitors or anti-VEGF angiogenic inhibitors, presented with diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri. Additional exclusion criteria were treatment with potent CYP3A4 inhibitors and inducers within 7-12 days of study treatment, concomitant treatment with therapeutic doses of anticoagulants, abnormal cardiac function such as abnormal ECGs, ongoing cardiac dysrhythmias, atrial fibrillation, or QTc prolongation  $>450$  for males and  $>470$  msec for females, LVEF  $\leq$  50%, and uncontrolled hypertension ( $>150/100$  mmHg).

##### **4.3.1.2. Randomization**

Subjects were randomized in a 1:1 fashion to receive either oral sunitinib or matching placebo; patients on both arms received best supportive care, beginning on Day 1 of the study. Investigators and subjects were blinded to treatment arm assignment until RECIST-

defined disease progression occurred or conclusion of the study. Randomization was balanced by country/region [grouped as Americas/Australia (Canada, US, Australia), Europe, Asia (Taiwan, Korea)], with a maximum of 180 subjects per region. The study was designed with a target sample size of 340 subjects.

#### **4.3.1.3. Study Treatment**

The starting dose of sunitinib was 37.5 mg administered once daily orally (on a CDD schedule). Subjects experiencing severe toxicity could receive treatment breaks inserted into the regimen as needed. Intrasubject dose reduction to 25 mg was permitted depending on toxicity. Intrasubject re-escalation of study medication back to a previous dose level was permitted at the discretion of the investigator upon consideration of the subject's clinical status. Dose escalation to 50 mg daily was recommended for subjects who had not yet achieved an objective disease response and who had not experienced progression or prohibitive toxicity.

No other approved or investigational anticancer treatments were permitted during the study period, including chemotherapy, biological response modifiers, hormone therapy, or immunotherapy. Use of somatostatin analogs for symptomatic control was permitted. This medication was recorded as a prior and concomitant medication.

Subjects were to be treated until progression of disease, unacceptable toxicity, or death.

#### **4.3.1.4. Crossover and Treatment on Extension Study**

During this study, subjects developing documented objective disease progression could be unblinded and, if assigned to placebo, offered access to treatment with open-label sunitinib in one of two companion extension trials (Study A6181114 or Study A6181078). Subjects who were unblinded at the time of disease progression and found to be receiving sunitinib were withdrawn unless assessed by the investigator as having the potential to experience clinical benefit from further treatment with sunitinib. In this case, the opportunity to receive open-label sunitinib in one of the extension studies may have been offered on an individual case basis. At the end of the study, remaining subjects were unblinded and offered access to open-label sunitinib in one of the extension studies.

#### **4.3.1.5. Efficacy Assessments**

Disease assessments were scheduled at the fixed time points indicated in the protocol. Care was taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays. Tumor imaging studies at screening included at least a CT or MRI scan of the chest, abdomen, and pelvis. Subsequent imaging studies were scheduled during week 5, week 9, and every 8 weeks thereafter, intervals sufficiently frequent to precisely estimate PFS and were required only for areas of known or suspected tumors. Additional disease assessments were performed if PD was suspected. Clinical assessments of disease were also scheduled at regular intervals. Brain CT or MRI and bone scan were performed at screening and repeated if metastases were present or suspected. The determination of tumor response and progression was made by the investigator and was based on objective tumor assessments made according to RECIST.

**Progression-Free Survival (PFS):** PFS, the protocol-specified primary endpoint, was defined as the time from date of randomization to the first objective PD or death due to any cause, whichever occurred first. Disease progression for the primary analysis was evaluated according to the RECIST by the investigator. PFS data were censored on the date of the last tumor assessment on study for subjects who did not have PD and who did not die while on study. For subjects who did not have a disease assessment after randomization, the endpoint was censored on the date of randomization with a duration of 1 day. Additionally, for subjects who started a new anti-cancer therapy prior to documented PD or who missed 2 consecutive tumor assessments before documented PD, the PFS data were censored at the date of the last tumor assessment documenting absence of PD.

PFS endpoint was evaluated in three ways:

1. Investigator Overall Tumor Assessment (IOTA): Investigator overall tumor assessments recorded in the electronic Case Report Forms (CRFs) were used to estimate PFS as reported in the initial sNDA pancreatic NET submission;
2. Algorithmic Assessment: At the request of FDA, Sponsor's analysis of Investigators' tumor measurements was used to derive tumor assessments utilizing a computer algorithm;
3. Blinded, Independent, Central Review (BICR): Performed per FDA request to address potential investigator bias in IOTA due to effective unblinding of known sunitinib-related AEs. The time point assessments made by the central radiological review were used to estimate PFS in conjunction with the clinical data regarding deaths and receipt of new anti-cancer therapy.

**Overall Survival (OS):** OS was defined as the time from the date of randomization to the date of death due to any cause. In the absence of death, OS was censored at the last date the subject was known to be alive. Information on survival status for subjects entering the extension studies (A6181114 or A6181078) is included in the analysis.

**Objective Response Rate (ORR):** ORR was defined as the percent of subjects experiencing a confirmed CR or PR according to RECIST. Confirmed responses were those that persisted on repeat imaging  $\geq 4$  weeks after initial documentation of response. ORR was calculated based on investigator overall tumor assessment and on algorithmic assessment.

**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 PD or to death due to any cause. DR was calculated only for the subgroup of subjects with an OR.

**Time to Tumor Response (TTR):** TTR was defined as the time from the date of randomization to the first documentation of objective tumor response (CR or PR) that was subsequently confirmed. An arithmetic median and range of TTR was provided in the subgroup of subjects with an objective tumor response. TTR was calculated based on investigator overall tumor assessment and on algorithmic assessment.

### ***Patient-Reported Outcomes***

***EORTC QLQ-C30*** : The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire-C30 (QLQ-C30, version 3), a validated self-administered questionnaire, was used to assess patient-reported outcomes. The EORTC QLQ-C30 measures 5 functional domains (physical, role, cognitive, emotional and social), a global health status/Quality of Life (QoL) scale, three multiple-item symptom scales (fatigue, nausea/vomiting, and pain), and 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact). EORTC QLQ-C30 scales were scored based on the EORTC recommendations as described in the EORTC QLQ-C30 scoring manual. All the domain scales and single-item scales range in score from 0 to 100 points. For the functional and global health status/QoL scale, higher scores represent a better level of functioning. For the symptoms scales, higher scores represented a greater degree or worsening of symptoms.

#### **4.3.1.6. Safety Assessments**

Safety evaluations included collection of AEs (from the first day of treatment to at least 28 days after the last dose of study drug) and assessment of clinical laboratory tests, 2-D echocardiograms or MUGA scans to determine LVEF, ECGs, vital signs, and ECOG performance status.

#### **4.3.1.7. Data Monitoring Committee**

The conduct of the study was overseen by an independent Data Monitoring Committee (DMC) to monitor the safety of the subjects on a periodic basis, approximately every six months, and to perform an interim analysis for safety, efficacy, futility and sample size re-estimation, if needed. The DMC panel of experts was without conflict of interest and reviewed emerging study results in an unblinded fashion. The DMC membership and governance was outlined separately in a DMC charter.

#### **4.3.1.8. Statistical Methods**

##### **4.3.1.8.1. Sample Size**

The initial target sample size was determined based on a 90% power to demonstrate a 50% improvement in median PFS using a 2-sided, unstratified log-rank test at a significance level of 0.05. The assumptions included a median PFS for placebo-treated subjects of 22 weeks, median PFS for sunitinib-treated subjects of 33 weeks, enrollment period of 26 weeks with an accrual rate of 13 subjects per week, and a 10% dropout rate. Approximately 340 subjects were required to observe 260 events (disease progression or death) assuming a 44-week follow-up after the last subject was enrolled.

The design included an interim efficacy analysis using the Lan-DeMets spending function with O'Brien-Fleming stopping boundaries to ensure the overall type I error, maintained at 0.05 for two-sided tests. The interim analysis was to be conducted when 50% of the PFS events required for the final analysis had occurred. The possibility of an increase in sample size based on the interim analysis was included.

#### 4.3.1.8.2. Analysis Population

***Intent-to-treat (ITT):*** The ITT population included 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 population was the primary population for evaluating subject characteristics and all efficacy endpoints except DR, analyzed in the subset of responders.

***As-treated (AT):*** The AT population included all subjects who received at least 1 dose of study treatment with assignment designated according to actual study treatment received. This population was the primary population for evaluating treatment administration/compliance and safety.

***Patient Reported Outcome (PRO) analysis set:*** The PRO population included subjects from the ITT population who completed baseline plus at least one on-study EORTC QLQ-C30 assessment. This analysis set was the primary analysis for evaluating PRO endpoints.

#### 4.3.1.8.3. Statistical Analysis

##### 4.3.1.8.3.1. PFS estimation based on Investigator Overall Tumor Assessment

In the initial submission, analysis of PFS was based on the overall tumor assessments (ie CR, PR, SD, PD) reported by the investigators (IOTA). This analysis is supplemented by two sensitivity analyses per the Statistical Analysis Plan (SAP):

Sensitivity analysis 1 corrected for potential bias in tumor assessment schedules by assigning dates for events only to scheduled visit dates.

Sensitivity analysis 2 expanded the definition of PFS events to include global deterioration of health, administration of a new anti-tumor treatment, and PD or death immediately after two or more missing assessments, which were all considered non-events and censored in the primary analysis.

The unstratified log-rank test was used to evaluate the primary efficacy endpoint, PFS, in the ITT population in these analyses.

##### 4.3.1.8.3.2. PFS estimation based on Algorithmic Assessment

The Algorithmic Assessment was a re-estimation of PFS based upon Sponsor's analysis of investigators' tumor measurements, according to RECIST; with the censoring rules for missing and incomplete assessments as specified in the SAP, following the FDA's "Guidance for Industry: Clinical Trial endpoints for the Approval of Cancer Drugs and Biologics, May 2007". In this analysis, the assessment of PD for each time point assessment was determined by the algorithm described in the Table 11 below.

**Table 11. Algorithm for the Assessment of PD in Pivotal Phase III Study A6181111**

Target Lesions	Non-Target Lesions	New Lesion	Algorithmic Assessment
≥20% increase in SLD (using investigator measurements) from nadir	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
Non-PD	Non-PD	No	Non-PD
NE	Non-PD	No	NE

Abbreviations: PD = Progressive Disease; Non-PD = any evaluation that is not progressive disease; NE = Not Evaluable.

Additional conventions were applied in this analysis and include the following.

- If one or more target lesion measurements was missing or recorded as “Indeterminate” at a time point, then the target lesion assessment for that time point was assigned as Not Evaluable (NE).
- If a target lesion was reported as “Too Small to Measure,” then a measurement of 5 mm for that target lesion was used in the calculation for target lesion response.
- Assessment of non-target lesions could be reported as a) “Absent” or “Present/Not Increased,” b) “Increased”, or c) “Indeterminate” in the study database. If all non-target lesions were assessed as “Absent” or “Present/Not Increased,” then the overall tumor assessment for non-target lesions at that time point was assigned as Non-PD.
- To determine whether increases in individual non-target lesions represented “unequivocal progression of non-target lesions” or not, the investigator overall assessment for non-target lesions [as reported on the Investigator Overall Tumor Assessment (IOTA) eCRF page] was used for the assigned assessment if one or more non-target lesions was recorded as “Increased.”
- If there were no non-target lesions recorded at baseline, or if one or more non-target lesion assessments was missing or recorded as “Indeterminate,” then the overall assessment for that time point was based on the assessment of the target lesions.

The Algorithmic Assessment analysis of PFS is supplemented by 3 sensitivity analyses (numbered as sensitivity analyses 3, 4 and 5).

In sensitivity analysis 3, non-target lesions were handled more conservatively, such that any non-target lesion assessment of “increased” was considered as indicating both unequivocal progression of non-target lesions and an overall assessment of progressive disease. The algorithm for determination of each algorithmic assessment is summarized in the following Table 12.

**Table 12. Based on Sensitivity Analysis 3 - Algorithm for the Determination of each Algorithmic Assessment in Pivotal Phase III Study A6181111**

Target Lesions	Non-Target Lesions	New Lesion	Algorithmic Assessment
≥20% increase in SLD (using investigator measurements) from nadir	Any	Any	PD
Any	Increased <sup>a</sup>	Any	PD
Any	Any	Yes	PD
Non-PD	Non-PD	No	Non-PD
NE	Non-PD	No	NE
Non-PD	NE	No	NE

Abbreviations: PD = Progressive Disease; non-PD = Any evaluation that is not progressive disease; NE = Not Evaluable

<sup>a</sup> For one or more non-target lesions.

Sensitivity analyses 4 and 5 were similar to sensitivity analyses 1 and 2, except that they were performed on the Algorithmic Assessment of PFS based on tumor measurement data used in the re-estimation rather than the PFS assessment based on investigator's overall tumor assessment used in the initial submission.

#### 4.3.2. Study Conduct

##### 4.3.2.1. DMC Reviews

The independent DMC first met on 13 March 2008 to establish the DMC charter and the list of tables for review. Subsequently, the DMC met 3 times to review safety data in May 2008, November 2008, and February 2009. The unblinded summary tables available to the DMC included subject enrollment by country and center, demographic characteristics, summary of PFS analysis, summary of treatment-emergent AEs by MedDRA SOC classification, preferred term, and maximum CTCAE grade (all causality, all cycles), summary of SAEs, and summary of results of laboratory data (hematology and chemistry, all cycles), by maximum CTCAE grade. In addition to safety data, the DMC had requested efficacy data to be included for their safety reviews. Efficacy endpoints of disease progression and death were indicative of risk in their benefit/risk analysis, therefore, were examined with the intent of assessing safety.

##### 4.3.2.2. DMC Recommendation

In February 2009, the independent DMC recommended that the study be closed based on its review of preliminary safety and efficacy data after only 73 PFS events had been recorded. The DMC determined that the study had met its primary endpoint in demonstrating a significant advantage for sunitinib. This recommendation was based on the observation of a median PFS of 11.1 months on the sunitinib arm versus 5.5 months on the placebo arm (hazard ratio of 0.397 [95% CI: 0.243, 0.649] and a 2-sided p-value <0.001) as of 25 February 2009. The DMC noted that conditional power predicted that if the study continued as planned and the interim analysis performed at 130 events, there would have been a 91% chance for stopping the study (for p<0.0031) assuming the upper limit of the 95% confidence interval of the observed hazard ratio (0.649) was the true hazard ratio, and an even greater

chance (99.9%) for stopping the study if the observed hazard ratio (HR=0.397) was the true hazard ratio. In addition, there were more deaths observed in placebo arm (15 deaths) than in sunitinib arm (5 deaths), and more SAE cases in placebo arm (28 cases) than in sunitinib arm (20 cases).

The decision by the DMC to recommend study termination was made out of concern for the welfare of subjects in the placebo arm of the study, given the magnitude of the treatment effect in PFS and the difference in deaths and SAEs observed between the two treatment arms. The sponsor agreed with the DMC recommendation, and in March 2009, notified all investigators that the study would be closed, and that all subjects should be offered open-label sunitinib on 1 of 2 extension studies (A6181078 or A6181114). The last subject visit on Study A6181111 occurred on 15 April 2009, the database was locked on 17 July 2009, and the final efficacy analysis was conducted based upon all PFS and OS events that had occurred by 15 April 2009.

### **4.3.3. Subject Characteristics in Pivotal Phase III Study A6181111**

#### **4.3.3.1. Subject Disposition**

The ITT population for pivotal Phase III Study A6181111 included 171 subjects, 86 subjects randomized to sunitinib and 85 subjects randomized to placebo. Subjects were enrolled from 42 sites in 11 countries. The AT population included 165 subjects, 83 in the sunitinib arm and 82 in the placebo arm; 3 subjects in each treatment arm did not receive study treatment (5 due to the study termination, 1 due to ineligibility).

The most common reasons for discontinuation were objective disease progression or relapse [19 (22.1%) sunitinib subjects vs. 47 (55.3%) placebo subjects; Table 13], study terminated by sponsor [41 (47.7%) sunitinib subjects vs. 16 (18.8%) placebo subjects], and AE [15 (17.4%) sunitinib subjects vs. 7 (8.2%) placebo subjects]. More subjects in the placebo arm discontinued from study due to disease progression, while study termination led to the treatment discontinuation of more subjects in the sunitinib arm, reflecting the greater number of ongoing subjects in the sunitinib arm. As expected with the treatment, occurrence of an AE led to the discontinuation of twice as many subjects in the sunitinib arm compared to the placebo arm. Other reasons that led to treatment discontinuation were global deterioration of health status, death of the subject, protocol violation, refusal of the subject for continued treatment for reason other than AE, other, lost to follow-up, and withdrawn due to pregnancy.

The median duration of follow-up, estimated using the reverse Kaplan-Meier approach (where death was censored and “remaining alive” was an event), was 10.2 (95% CI: 8.1 - 12.6) months and 11.1 (95% CI: 9.0 - 12.5) months for the sunitinib and placebo arms, respectively. The median potential follow-up time (defined as the time from randomization to study termination on 15 April 2009) was 12.3 (range: 0.0 - 21.0) months and 12.4 (range: 0.3 - 22.1) months for the sunitinib and placebo arms, respectively.

**Table 13. Subject Disposition in the ITT Population – Phase III Study A6181111**

<b>Reason for Discontinuation</b>	<b>Sunitinib N = 86</b>	<b>Placebo N = 85</b>
Randomized But Not Treated	3 (3.5)	3 (3.5)
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 AE	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

Abbreviations: N = number of subjects; AE = adverse event; AT = as-treated population.  
 Source: CSR Study A6181111

**4.3.3.2. Demography, Baseline Characteristics, Disease Characteristics, and Prior Treatment - Phase III Study A6181111**

Baseline characteristics including age, gender, race, and ECOG performance status were generally comparable between the sunitinib and placebo arms. More than half of all subjects (48; 55.8%) in the sunitinib arm and in the placebo arm (53 subjects 62.4%) were white (Table 14). All subjects had an ECOG PS of 0 or 1 at baseline, with the exception of 1 subject on the placebo arm who had an ECOG PS of 2; the enrollment of this subject was a protocol deviation. The proportion of subjects with ECOG PS of 0 was higher on the sunitinib arm (61.6%) than on the placebo arm (48.2%).

Approximately half of the subjects had nonfunctioning tumors. Liver, pancreas, and lymph node were the most commonly involved sites of disease. Approximately 89% of subjects in each treatment arm had prior surgical treatment, and the majority of subjects (66.3% and 71.8% in the sunitinib and placebo arms, respectively) were previously treated with systemic therapies. Overall, the baseline disease characteristics and prior treatment history of the subjects were similar between the sunitinib arm and the placebo arm with the exception of time from diagnosis to study entry, which was 2.4 and 3.2 years in the sunitinib arm and placebo arm, respectively.

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**Table 14. Summary of Demography, Baseline Characteristics, Disease Characteristics, and Prior Treatment in ITT Population - Phase III Study A6181111**

	<b>Sunitinib (N = 86)</b>	<b>Placebo (N = 85)</b>
<b>Demography</b>		
Median Age [years] (Range)	56 (25 – 84)	57 (26 – 78)
Sex [n (%)]		
Male	42 (48.8)	40 (47.1)
Female	44 (51.2)	45 (52.9)
Race [n (%)]		
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)
<b>Baseline Characteristics</b>		
ECOG Performance Status [n (%)]		
0	53 (61.6)	41 (48.2)
1	33 (38.4)	43 (50.6)
2	0	1 (1.2)
<b>Disease Characteristics</b>		
Nonfunctioning Tumor [n (%)]	42 (48.8)	44 (51.8)
Functioning Tumor [n (%)]	25 (29.1)	21 (24.7)
Gastrinoma	9 (10.5)	10 (11.8)
Glucagonoma	3 (3.5)	2 (2.4)
Insulinoma	2 (2.3)	2 (2.4)
VIPoma	0	2 (2.4)
Other	11 (12.8)	5 (5.9)
Unknown/missing [n (%)]	19 (22.1)	20 (23.5)
Median duration since diagnosis [years (range )]	2.4 (0.1 – 25.6)	3.2 (0.1 – 21.3)
Involved disease sites [n (%)]		
Pancreas	35 (40.7)	31 (36.5)
Lymph node	29 (33.7)	41 (48.2)
Liver	79 (91.9)	78 (91.8)
Lung	9 (10.5)	15 (17.6)
Peritoneum	3 (3.5)	7 (8.2)
Stomach	0	1 (1.2)
Other	18 (20.9)	21 (24.7)
Presence of distant metastatic sites [n (%)]	82 (95.3)	80 (94.1)
<b>Prior Treatment</b>		
Prior surgery [n (%)]	76 (88.4)	77 (90.6)
Previous radiation therapy [n (%)]	9 (10.5)	12 (14.1)
Prior somatostatin analogue use	30 (34.9) <sup>a</sup>	32 (37.6) <sup>a</sup>

**Table 14. Summary of Demography, Baseline Characteristics, Disease Characteristics, and Prior Treatment in ITT Population - Phase III Study A6181111**

	<b>Sunitinib (N = 86)</b>	<b>Placebo (N = 85)</b>
Prior systemic therapies [n (%)]	57 (66.3)	61 (71.8)
Excluding chemoembolization and regimen with somatostatin analog only	45 (52.3)	50 (58.8)
Prior liver directed therapy [n (%)]		
Chemoembolization	7 (8.1)	14 (16.5)
Radiofrequency ablation	3 (3.5)	6 (7.1)
Alcoholization procedure	1 (1.2)	2 (2.4)

Abbreviations: N = Total number of subjects included in the treatment population; n = number of subjects;

<sup>a</sup>Includes somatostatin analogues reported as prior systemic therapy or as concomitant medication with the start date preceding the first dose.

Source: CSR Study A6181111

#### 4.3.3.3. Exposure to Drug in Pivotal Phase III Study

The median number of days on study was higher on the sunitinib arm (141 days, range 13-602 days; Table 15) compared to the placebo arm (113 days, range 1-614 days). Nineteen subjects (22.9%) on the sunitinib arm and 3 subjects (3.7%) on the placebo arm were on study for >1 year.

The median number of cycles started was greater on the sunitinib arm (5 cycles) compared to the placebo arm (4 cycles). The number of subjects with at least 1 dose interruption and the number of subjects with at least 1 dose reduction was greater on the sunitinib arm (25 subjects with an interruption and 26 subjects with a reduction) than on the placebo arm (10 subjects with an interruption and 9 subjects with a reduction). The overall mean relative dose intensity (RDI; the percentage of actual to intended dose intensities) was 91.3% for the sunitinib arm and 100.6% for the placebo arm. For the sunitinib arm, mean RDI ranged from 85.2% to 95.7% in each cycle from cycles 1-9; mean RDI in cycles 10-20 was generally ≤85%. Misunderstandings in dosing instructions were reported for 3 subjects in the placebo arm; each received more capsules of blinded therapy than prescribed in the protocol for short periods of time.

**Table 15. Exposure to Study Drug in the ITT Population - Phase III Study A6181111**

Variable	Sunitinib N = 83	Placebo N = 82
Number of days on study		
Median duration (days)	141	113
Range (days)	13-602	1-614
Number of cycles started	591	436
Median Number of cycles started	5	4
Range	1-20	1-22
Number (%) subjects with at least 1 dose interruption <sup>a</sup>	25 (30.1)	10 (12.2)
Total Number of Dose Interruption:		
1 to <2 weeks	30	6
2 to <3 weeks	16	2
≥3 weeks	4	4
Reasons for Dose Interruption:		
AE	31	22
Other	3	7
AE and other (both)	9	5
Number (%) of subjects with at least 1 Dose Reduction <sup>b</sup>	26 (31.3)	9 (11.0)
Total Number of Dose Reductions, number (%) of subjects:		
1 reduction	24 (28.9)	9 (11.0)
≥2 reductions	2 (2.4)	0
Reason for Dose Reduction:		
AE	24	8
Other	1	4
AE and other (both)	1	1
Number (%) of Subjects with at least 1 Dose Escalation <sup>c</sup>	8 (9.6)	20 (24.4)
Relative dose intensity <sup>d</sup> (%)		
Median (range)	99.8 (55.3-125.7)	100.0 (70.4-145.5)
Mean (standard deviation)	91.3 (14.7)	100.6 (13.0)

Abbreviations: N = Number of subjects

<sup>a</sup> An interruption of 7 days or more was considered to be a dose interruption. For dose interruption categories, 1- <2 weeks was 7-13 days, 2-<3 weeks was 14-20 days and ≥3 weeks was at least 21 days of interruption

<sup>b</sup> A single dose reduction was from 37.5 to 25 mg or from 50 to 37.5 mg. A dose reduction from 50 to 25 mg was counted as 2 dose reductions; <sup>c</sup> A single dose escalation was from 37.5 to 50 mg; <sup>d</sup> Relative dose intensity >100% reflects a dose escalation to 50 mg.

<sup>c</sup> A single dose escalation was from 37.5 to 50 mg

<sup>d</sup> Relative dose intensity >100% reflects a dose escalation to 50 mg.

Source: CSR Study A6181111

#### 4.3.4. Efficacy Results in Pivotal Phase III Study A6181111

##### 4.3.4.1. Primary Endpoint - Progression-Free Survival

###### 4.3.4.1.1. PFS Estimation Based on Investigator Overall Tumor Assessment

The primary endpoint PFS was prolonged after treatment with sunitinib in subjects with progressive, well-differentiated pancreatic islet cell tumors. The median PFS was 11.4

months in the sunitinib arm compared to 5.5 months in the placebo arm (hazard ratio, HR = 0.418,  $P = 0.000118$  for the 2-sided unstratified log-rank test; Table 16).

The probability of being event-free at 6 months was 71.3% for the sunitinib arm and 43.2% for the placebo arm. The Kaplan-Meier plots of PFS are shown in Figure 5. The Kaplan-Meier plot demonstrated separation of PFS curves between treatment arms beginning early in the study and persisting over time, and with the control arm performing as predicted. Although the  $P$  value ( $P = 0.000118$ ) was less than the pre-specified overall Type I error rate for this trial ( $\alpha = 0.05$ ), the number of PFS events was also lower than initially designed, and handling of multiple efficacy data by the DMC was not pre-specified (only 1 interim analysis per the SAP). Thus, the nominal critical value ( $Z$  scale) to establish statistical significance for the final analysis was calculated using the Lan-DeMets spending function both excluding and including 3 data looks by the DMC during their safety reviews [May 2008 (20 PFS events), November 2009 (50 events), and February 2009 (73 PFS events)]. The nominal critical  $Z$  value for the final analysis with 81 PFS events without adjusting for the 3 data looks was 3.8494 (Table 17); however, adjusting for the 3 data looks resulted in a nominal critical  $Z$  value of 3.8809. The observed test statistic in the final analysis was 3.8506. Under the more conservative approach of adjusting for 3 data looks, the test statistic, although very close, did not cross the efficacy boundary.

**Table 16. Initial Analyses of Progression-Free Survival Based on Investigator Overall Tumor Assessment in ITT Population - Phase III Study A6181111**

	Initial PFS Analysis		Sensitivity Analysis of PFS			
	Sunitinib (N=86)	Placebo (N=85)	Analysis 1		Analysis 2	
			Sunitinib (N=86)	Placebo (N=85)	Sunitinib (N=86)	Placebo (N=85)
Number with Event	30	51	30	51	30	55
Type of Event						
Objective tumor progression	27	48	27	48	27	48
Death without objective PD	3	3	3	3	3	2
Symptomatic deterioration	---	---	---	---	0	5
Number censored	56	34	56	34	56	30
Probability of being event-free at Month 6 <sup>a</sup> (95% CI <sup>b</sup> )	71.3% (60.0, 82.5)	43.2% (30.3, 56.1)	67.5% (55.7, 79.4)	41.5% (28.6, 54.4)	71.3% (60.0, 82.5)	39.8% (27.5, 52.2)
Kaplan-Meier estimates of Median PFS (months) (95% CI) <sup>c</sup>	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	11.1 (7.4, --)	5.5 (3.6, 7.4)	11.4 (7.4, 19.8)	5.4 (3.6, 7.3)
Sunitinib vs. Placebo Hazard ratio <sup>d</sup> (95% CI)	0.418 (0.263, 0.662)		0.407 (0.257, 0.646)		0.393 (0.250, 0.620)	
Log-Rank test statistic <sup>e</sup>	3.8506		3.9751		4.1945	
P value <sup>e</sup>	0.000118		0.000070		0.000027	

Abbreviations: N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease; CI = confidence interval; ITT = intent to treat

<sup>a</sup> Estimated from the Kaplan-Meier curve

<sup>b</sup> Calculated from the product-limit method

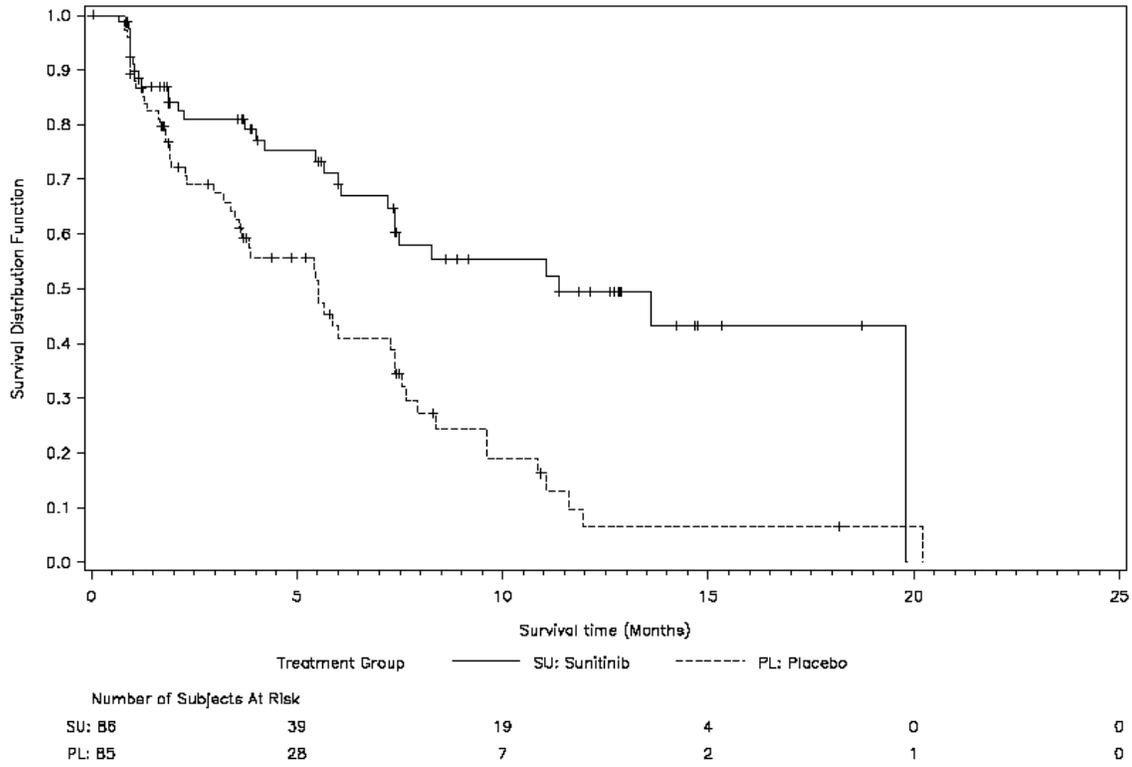
<sup>c</sup> Based on the Brookmeyer-Crowley method

<sup>d</sup> Based on the Cox proportional hazards model

<sup>e</sup> Log-rank test statistic and 2-sided p-value from the unstratified log-rank test

Source: CSR Study A6181111

**Figure 5. Kaplan-Meier Curves of Progression-Free Survival in ITT Population Based on Investigator Overall Tumor Assessment – Phase III Study A6181111**



Source: CSR Study A6181111

**Table 17. Statistical Boundaries and Observed Test Statistics**

	Investigator Overall Tumor Assessment 81 Observed Events		Algorithmic Assessment 79 Observed Events	
	Z Scale	P value	Z Scale	P value
Efficacy boundary without adjustment for 3 data looks	3.8494	0.000119	3.9016	0.000096
Efficacy boundary adjusted for 3 data looks	3.8809	0.000104	3.9402	0.000081
Observed test statistic	3.8506	0.000118	3.9890	0.000066

Source: Test statistic is from CSR Study A6181111; efficacy boundary is calculated based on pre-specified Lan-DeMets boundary using statistics software EAST5.1.

**4.3.4.1.2. PFS Estimation Based on Algorithmic Assessment**

Analysis of PFS based on algorithmic assessment data also demonstrated a clinically prolonged median PFS of 12.6 months in the sunitinib arm and 5.4 months in the placebo arm (HR = 0.401,  $P = 0.000066$  from the 2-sided unstratified log-rank test; Table 17). This analysis of PFS included 79 events corresponding to a critical Z value from the O'Brien-

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Fleming efficacy boundary of 3.9402 when adjusting for 3 data looks (Table 17). The observed test statistic in this PFS analysis was 3.9890 and was greater than the critical Z value. The Kaplan-Meier plots of PFS are shown in Figure 6.

Sensitivity analyses for PFS were performed to test the robustness of the primary PFS analysis based on the IOTA and Algorithmic Assessment PFS estimation methods. As described earlier (See Section 4.3.1.8.3), sensitivity analysis 1 and 4 corrected for potential bias in tumor assessment dates; sensitivity analysis 2 and 5 included additional clinical outcomes as PFS events and sensitivity analysis 3 consisted of a more conservative definition of disease progression due to non-target lesions. Each of these sensitivity analyses demonstrated a similar treatment effect as observed in the primary analysis. The results for the sensitivity analyses are summarized in Tables 16 and 18 for IOTA and Algorithmic Assessment, respectively.

**Table 18. Re-Analysis of Progression-Free Survival in ITT Population Based on Algorithmic Assessment – Phase III Study A6181111**

	PFS Analysis Based on Algorithmic Assessment		Sensitivity Analysis of PFS				Analysis 3 <sup>h</sup>	
	Sunitinib (N=86)	Placebo (N=85)	Analysis 4 <sup>f</sup>		Analysis 5 <sup>g</sup>		Sunitinib (N=86)	Placebo (N=85)
			Sunitinib (N=86)	Placebo (N=86)	Sunitinib (N=86)	Placebo (N=85)		
Number with Event	30	49	30	49	30	52	30	49
Type of Event								
Objective tumor progression	27	46	27	46	27	46	28	47
Death without objective PD	3	3	3	3	3	2	2	2
Symptomatic deterioration	---	---	---	---	0	4	---	---
Number censored	56	36	56	36	56	33	56	36
Probability of being event-free at Month 6 <sup>a</sup> (95% CI <sup>b</sup> )	74.4% (63.2, 85.6)	38.8% (25.9, 51.6)	72.7% (61.2, 84.2)	37.1% (24.3, 49.9)	74.4% (63.2, 85.6)	36.2% (23.8, 48.6)	73.7% (62.2, 85.2)	35.7% (23.0, 48.4)
Kaplan-Meier estimates of Median PFS (months) (95% CI) <sup>c</sup>	12.6 (7.4, 16.9)	5.4 (3.5, 6.0)	11.0 (7.4, 16.6)	5.4 (3.6, 5.8)	12.6 (7.4, 16.9)	4.9 (3.5, 5.8)	11.4 (7.4, 16.9)	3.8 (3.4, 5.8)
<u>Sunitinib vs. Placebo</u>								
Hazard ratio <sup>d</sup> (95% CI)	0.401 (0.252, 0.640)		0.401 (0.252, 0.639)		0.38 (0.240, 0.602)		0.410 (0.257, 0.653)	
Log-Rank test statistic <sup>e</sup>	3.9890		4.0211		4.2970		3.8950	
<i>P</i> value <sup>e</sup>	0.000066		0.000058		0.000017		0.000098	

Abbreviations: N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease; CI = confidence interval; ITT = intent to treat

<sup>a</sup> Estimated from the Kaplan-Meier curve

<sup>b</sup> Calculated from the product-limit method

<sup>c</sup> Based on the Brookmeyer-Crowley method

<sup>d</sup> Based on the Cox proportional hazards model

<sup>e</sup> Log-rank test statistic and 2-sided p-value from the unstratified log-rank test

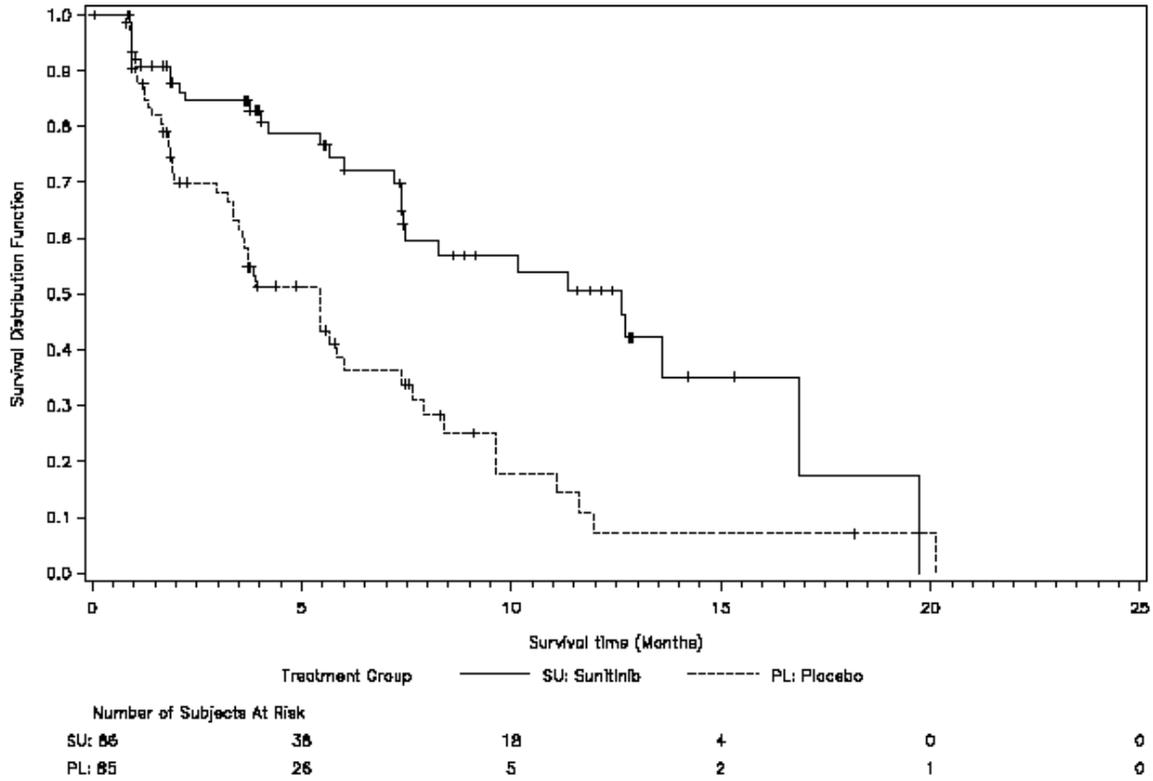
<sup>f</sup> similar to sensitivity analysis 1: corrected for potential bias in tumor assessment dates

<sup>g</sup> Similar to sensitivity analysis 2: included additional clinical outcomes as PFS events

<sup>h</sup> Consist of a more conservative definition of disease progression due to non-target lesions.

Source: CSR Supplement Study A6181111

**Figure 6. Kaplan-Meier Curves of Progression-Free Survival in ITT Population Based on Algorithmic Assessment – Phase III Study A6181111**



Source: CSR Study A6181111

**4.3.4.1.3. PFS Estimation Based on Blinded Independent Central Review**

An additional PFS analysis on all randomized subjects based on Blinded Independent Central Review (BICR) assessments was performed using all scans collected. Scans from 99.4% of the study population with all scans for all time points available for 93.6% of the study subjects were retrieved. Results of the BICR analysis are provided in Table 19. Assessment of PFS based upon BICR included 61 PFS events and demonstrated a median PFS of 12.6 months in the sunitinib arm and 5.8 months in the placebo arm (HR = 0.315, 95%CI: 0.181, 0.546,  $P = 0.000015$ ; Table 19). The impact of missing scans to PFS analysis was minimal and did not change the interpretation of the treatment effect of sunitinib, which further supported the robustness of the BICR PFS analysis. The Kaplan-Meier analysis based on BICR assessment is presented in Figure 7.

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**Table 19. Analysis of Progression-Free Survival in ITT Population Based on BICR Analysis – Phase III Study A618111**

	BICR Analysis	
	Sunitinib (N=86)	Placebo (N=85)
Number with event	22	39
Type of event		
Objective tumor progression	19	34
Death without objective PD	3	5
Number censored	64	46
Kaplan-Meier estimates of median PFS (months) (95% CI) <sup>a</sup>	12.6 (11.1, 20.6)	5.8 (3.8, 7.2)
Sunitinib vs. Placebo		
Hazard ratio <sup>b</sup> (95% CI)	0.315 (0.181, 0.546)	
P value <sup>c</sup>	0.000015	

Abbreviations: N = number of subjects randomized; PFS = progression-free survival; PD = progressive disease; CI = confidence interval; ITT = intent to treat

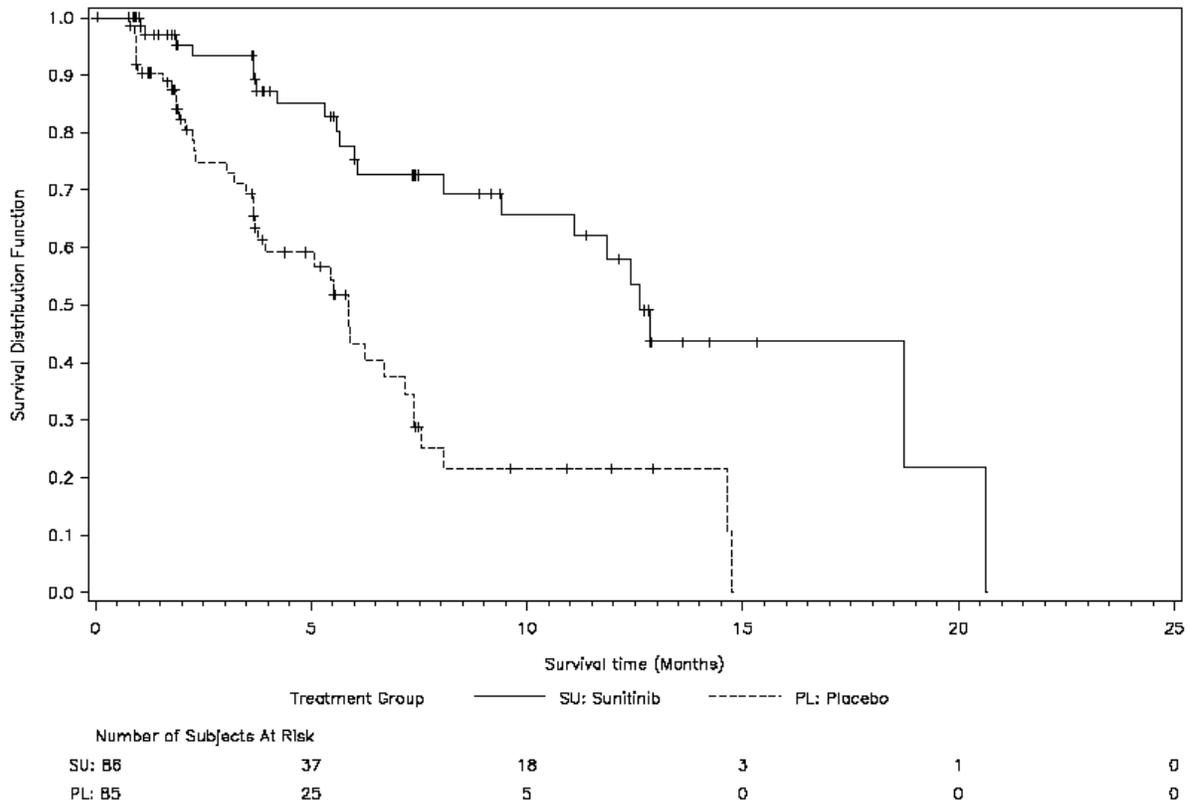
<sup>a</sup> Based on the Brookmeyer-Crowley method

<sup>b</sup> Based on the Cox proportional hazards model

<sup>c</sup> Log-rank test statistic and 2-sided p-value from the unstratified log-rank test.

Source: BICR Report

**Figure 7. Kaplan-Meier Curves of Progression-Free Survival in ITT Population Based on BICR Analysis – Phase III Study A618111**



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Source: BICR Report

Because the BICR was a blinded, independent central review and not an independent verification of investigator tumor measurements, it was expected that the choice of target and non-target lesions by investigators and the radiologists conducting the BICR would be different for the majority of cases. Confirmation of investigator tumor measurements from BICR data is not feasible. Nevertheless, a comparison of the Algorithmic Assessment derived from investigator tumor measurements against BICR assessments was conducted and the results argue against the introduction of systematic bias in the Algorithmic Assessment.

#### 4.3.4.1.4. Comparison of 3 PFS Analyses

In summary, the primary efficacy results from Study A6181111 demonstrated a clear and clinically significant advantage for sunitinib treatment over placebo in subjects with well-differentiated pancreatic NET, who had recent disease progression (< 12 months). Improvement in PFS was consistent across all subgroups and was independent of any differences in baseline characteristics examined with exception of time from diagnosis, which favored the placebo arm as prognostically better. A summary of PFS evaluated by 3 different methods in the ITT population is shown in Table 20. The overlaid Kaplan-Meier plots of PFS by 3 methods is depicted in Figure 8.

**Table 20. Summary of Progression-Free Survival Evaluated in 3 Ways in ITT Population - Phase III Study A6181111**

	Phase III Study A6181111					
	Investigator Overall Tumor Assessment		Algorithmic Assessment		BICR	
	Sunitinib (N=86)	Placebo (N=85)	Sunitinib (N=86)	Placebo (N=85)	Sunitinib (N=86)	Placebo (N=85)
Number of Events	30	51	30	49	22	39
Number censored	56	34	56	36	64	46
Median (95% CI) <sup>a, b</sup> (months)	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	12.6 (7.4 – 16.9)	5.4 (3.5 – 6.0)	12.6 (11.1, 20.6)	5.8 (3.8, 7.2)
Hazard ratio (sunitinib vs. placebo) (95% CI) <sup>c</sup> <i>P</i> value <sup>d</sup>	0.418  (0.263, 0.662) 0.000118		0.401  (0.252, 0.640) 0.000066		0.315  (0.181, 0.546) 0.000015	

Abbreviations: N = number of subjects randomized; PFS = progression-free survival; CI = confidence interval; NA = not applicable; BICR = Blinded Independent Central Review; ITT = intent to treat

<sup>a</sup> Estimated from the Kaplan-Meier curve

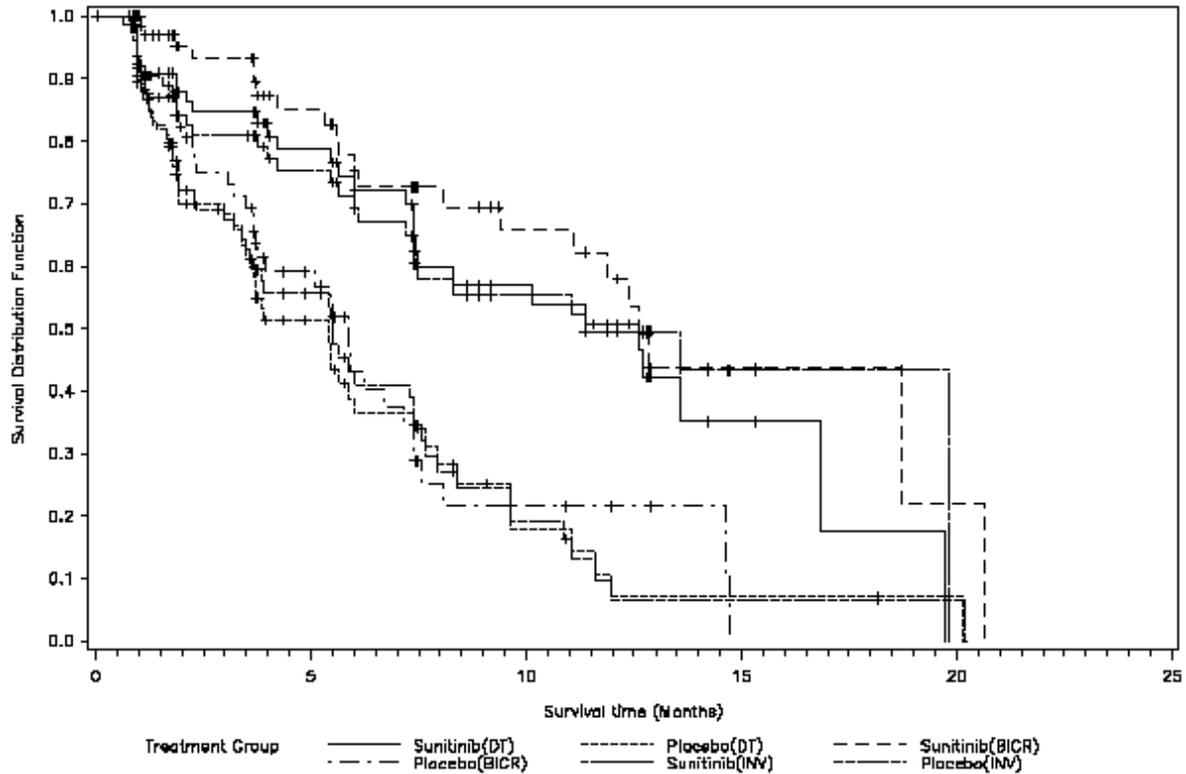
<sup>b</sup> Based on the Brookmeyer-Crowley method;

<sup>c</sup> Based on the Cox proportional hazards model

<sup>d</sup> 2-sided *P* value from the unstratified log-rank test.

Source: CSR Study A6181111; BICR Report

**Figure 8. Kaplan-Meier Plots of Progression-Free Survival (Investigator Overall Tumor Assessment vs. Algorithmic Tumor Assessment vs. BICR Assessment) – Intent-to-Treat Population**



Source: Summary of Clinical Efficacy

#### 4.3.4.1.5. Influence of Baseline Characteristics in PFS Estimation

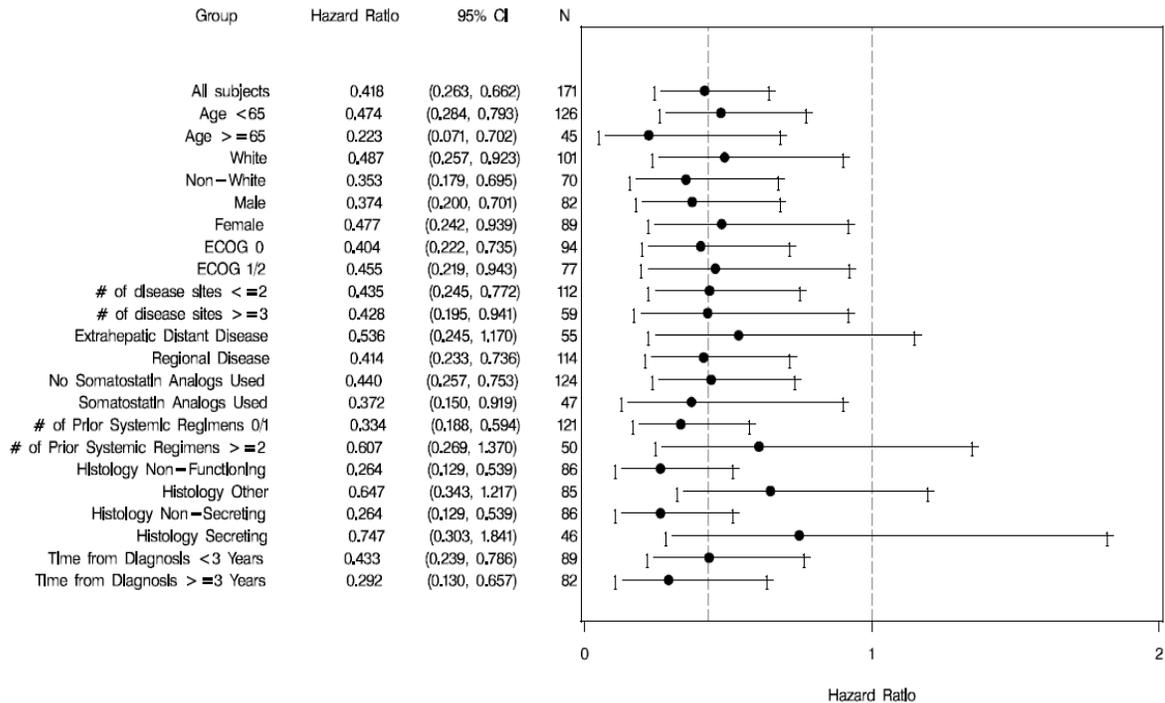
The influence of baseline characteristics on the treatment effect was analyzed for the primary endpoint PFS. The characteristics evaluated were:

- baseline age (<65 vs.  $\geq 65$  years),
- race (white vs. non-white [including Asian, Other, and Unspecified]),
- gender (male vs. female),
- baseline ECOG performance status (0 vs. 1 or 2),
- number of disease sites at baseline (defined as the number of organs involved, regardless of number of lesions per organ  $\leq 2$  vs.  $\geq 3$ ),
- disease extent (extrahepatic distant disease vs. regional disease [defined as disease limited to the pancreas, lymph nodes, and/or liver]),
- somatostatin analogs used regardless of timing relative to study treatment (yes vs. no),
- number of prior systemic regimens used [defined here as those regimens not administered intra-arterially and not consisting solely of a somatostatin analog; regimens could include one or more agents] (<2 vs.  $\geq 2$ ),

- histology (nonfunctioning [as reported by the investigator] vs. other [including those reported as unknown]),
- histology (non-secreting [defined as those reported as nonfunctioning] vs. secreting [defined as those reported as other than nonfunctioning or unknown]), and
- time from diagnosis (3 years vs.  $\geq 3$  years).

The results showed that the hazard ratio favored sunitinib in all subgroups, and it was statistically significant in all subgroups except in extrahepatic distant disease, number of prior systemic regimens  $\geq 2$ , histology other than nonfunctioning, and histology secreting subgroups. The results shown in Figure 9 are based on investigator overall tumor assessment analysis.

**Figure 9. Results of Cox Proportional Hazards Analysis of Progression-Free Survival in ITT Population Based on Investigator Overall Tumor Assessment – Phase III Study A6181111**



Source: CSR Study A6181111

Note: Sunitinib arm vs placebo arm: assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the sunitinib arm; a hazard ratio greater than 1 indicates a reduction in hazard rate in favor of the placebo arm.

Non-White includes subjects for whom race was not recorded due to local regulations.

Regional disease includes subjects for whom disease was limited to the pancreas, lymph node (of any location), and liver.

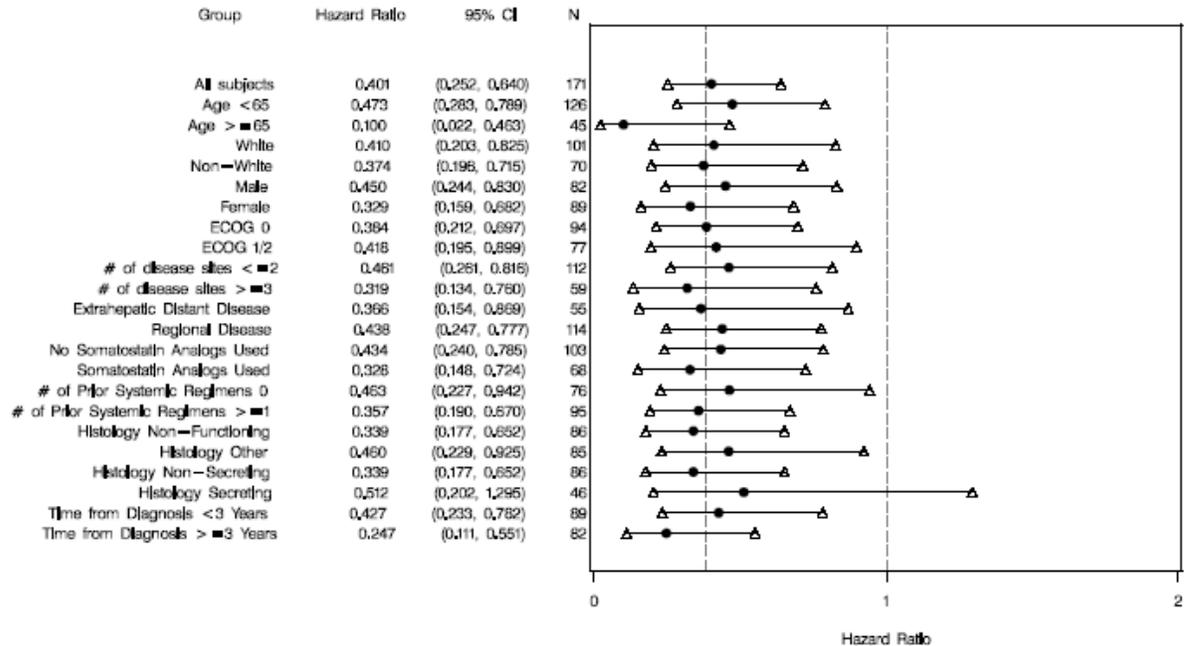
Somatostatin analog used includes subjects treated before and/or during the study.

Nonfunctioning was reported by the investigator.

Histology other includes subjects with secreting tumor and tumor unknown secreting status.

The analysis of the influence of baseline characteristics on PFS was repeated using Algorithmic Assessment based on investigators' tumor measurements. In this analysis, the hazard ratio also favored treatment with sunitinib, and was statistically significant in all subgroups except the subgroup of subjects with secreting tumors. The results are shown in Figure 10.

**Figure 10. Results of Cox Proportional Hazards Analysis of Progression-Free Survival in ITT Population Based on Algorithmic Tumor Assessment – Phase III Study A6181111**



Source: CSR Supplement Study A6181111

Note: Sunitinib arm vs placebo arm: assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the sunitinib arm; a hazard ratio greater than 1 indicates a reduction in hazard rate in favor of the placebo arm.

Non-White includes subjects for whom race was not recorded due to local regulations.

Regional disease includes subjects for whom disease was limited to the pancreas, lymph node (of any location), and liver.

Somatostatin analog used includes subjects treated before and/or during the study.

Nonfunctioning was reported by the investigator.

Histology other includes subjects with secreting tumor and tumor unknown secreting status.

The influence of baseline factors on the treatment effect was further analyzed by using a Cox proportional hazards model including the baseline factors, controlling for each factor one at a time in the ITT population. The results showed that the hazard ratio for the overall treatment effect was 0.418 (95% CI: 0.263, 0.662) and 0.401 (95% CI: 0.252, 0.640) based on investigator overall tumor assessment and algorithmic assessment, respectively, and was similar when controlling for each individual baseline factor.

All the baseline factors were entered into multivariate models and only factors with *P* values < 0.05 following backward selection were retained in the final model. The final model for PFS using Cox proportional hazards analysis in the ITT population revealed that treatment (sunitinib vs. placebo) and time from diagnosis ( $\geq 3$  vs. < 3 years) were the only baseline factors retained regardless of whether tumor assessment was investigator-reported or algorithmic, as summarized in Table 21.

**Table 21. Multivariate Model for Progression-Free Survival – Intent-To-Treat Population**

Model	Hazard Ratio	95% CI	<i>P</i> value
Investigator overall tumor assessment			
Treatment (sunitinib vs. placebo)	0.374	0.234 to 0.599	< 0.0001
Time from diagnosis ( $\geq 3$ vs. < 3 years)	0.603	0.382 to 0.952	0.0299
Algorithmic assessment			
Treatment (sunitinib vs. placebo)	0.359	0.224 to 0.576	< 0.0001
Time from diagnosis ( $\geq 3$ vs. < 3 years)	0.545	0.344 to 0.863	0.0097

Abbreviations: CI = confidence interval.  
 Source: CSR Study A6181111

#### 4.3.4.1.6. PFS estimation based on Ki-67 Index

The Ki-67 protein is a marker for cellular proliferation that has been reported as a prognostic marker in pancreatic NET; thus, pre-treatment Ki-67 index was also analyzed as a separate baseline disease characteristic for the 72 subjects with an available record of Ki-67 index measured as a percentage. In order to determine whether the sunitinib treatment effect might be influenced by baseline Ki-67 status, exploratory analyses of PFS were conducted. Subjects were retrospectively stratified into two groups according to Ki-67 index. The median Ki-67 index was 5%, and the two groups consisted of those subjects with Ki-67 indices that were either  $\leq 5\%$  or  $> 5\%$ . Among subjects with Ki-67 indices  $\leq 5\%$ , Kaplan-Meier analysis demonstrated that PFS was significantly longer in the sunitinib arm (median PFS = 48.1 weeks, N = 23) than in the placebo arm (median PFS = 24.0 weeks, N = 20; hazard ratio = 0.378; log-rank *P* = 0.0259) based on investigator overall tumor assessment, as shown in Table 22. Similarly, based on algorithmic assessment, among subjects with Ki-67 indices  $\leq 5\%$  (N = 43), Kaplan-Meier analysis demonstrated that PFS was significantly longer in the sunitinib arm (median PFS = 55.3 weeks, N = 23; Table 23) than in the placebo arm (median PFS = 28.4 weeks, N = 20; hazard ratio = 0.362; log-rank *P* = 0.03613). Among subjects with Ki-67 indices  $> 5\%$  (N = 29), no significant difference in PFS was observed (hazard ratio = 0.634, log-rank *P* = 0.3638 based on investigator overall tumor assessment; hazard ratio = 0.438, log rank *P* = 0.1018 based on algorithmic assessment), although the number of events was small.

Additionally, Ki-67 indices were available for 3 of the 8 subjects in the sunitinib treatment arm who achieved a tumor response based on investigator overall tumor assessment, including one subject with a CR and two subjects with PRs. The Ki-67 index was 3% for the subject who had a CR, while Ki-67 indices were 2% and 25% for the two subjects with PRs. In the re-analysis of RECIST-defined tumor response based on algorithmic assessment, Ki-

67 indices were available for 5 of the 8 subjects in the sunitinib treatment arm who achieved a tumor response. All of these subjects had a PR, and their Ki-67 index values were 1%, 2%, 3%, 12% and 25%.

These exploratory analyses are consistent with a sunitinib treatment effect independent of level of Ki-67 staining and sunitinib-associated objective tumor response across a broad range of Ki-67 indices.

**Table 22. Comparison of PFS between Treatments in Subjects with Ki-67 Index ≤5% and Ki-67 Index >5% (Based on Investigator Overall Tumor Assessment)**

	Ki-67 ≤ 5%	Ki-67 > 5%
<b>Sunitinib</b>		
N	23	13
Median PFS <sup>a</sup> (weeks) (95% CI) <sup>b</sup>	48.1 (17.4 – 59.1)	9.7 (8.1 - <sup>c</sup> )
<b>Placebo</b>		
N	20	16
Median PFS <sup>a</sup> (weeks) (95% CI) <sup>b</sup>	24.0 (8.3 – 36.4)	14.7 (5.6 – 24.6)
<b>Hazard ratio<sup>c</sup> (sunitinib vs placebo) (95% CI)</b>	0.378 (0.155 – 0.922)	0.634 (0.235 – 1.711)
<i>P</i> value <sup>d</sup>	0.0259	0.3638

Abbreviations: N = number of subjects; CI = confidence interval; PFS = progression-free survival

<sup>a</sup> Kaplan-Meier estimate

<sup>b</sup> Based on the Brookmeyer-Crowley method

<sup>c</sup> Based on the Cox proportional hazards model

<sup>d</sup> 2-sided P value from the unstratified log-rank test

<sup>e</sup> Unable to calculate.

Source: CSR Study A6181111

**Table 23. Comparison of PFS between Treatments in Subjects with Ki-67 Index ≤5% and Ki-67 Index > 5% (Re-Analysis Based on Algorithmic Assessment)**

	Ki-67 ≤ 5%	Ki-67 > 5%
<b>Sunitinib</b>		
N	23	13
Median PFS <sup>a</sup> (weeks) (95% CI) <sup>b</sup>	55.3 (24.6 – 59.1)	23.7 (9.1 - <sup>c</sup> )
<b>Placebo</b>		
N	20	16
Median PFS <sup>a</sup> (weeks) (95% CI) <sup>b</sup>	28.4 (8.3 – 41.9)	14.7 (6.1 – 24.6)
<b>Hazard ratio<sup>c</sup> (sunitinib vs placebo) (95% CI)</b>	0.362 (0.134 – 0.981)	0.438 (0.158 – 1.2110)
<i>P</i> value <sup>d</sup>	0.0361	0.1018

Abbreviations: N = number of subjects; CI = confidence interval; PFS = progression-free survival

<sup>a</sup> Kaplan-Meier estimate

<sup>b</sup> Based on the Brookmeyer-Crowley method

<sup>c</sup> Based on the Cox proportional hazards model

<sup>d</sup> 2-sided P value from the unstratified log-rank test

<sup>e</sup> Unable to calculate.

Source: CSR Study A6181111

### 4.3.4.2. Secondary Efficacy Endpoints

#### 4.3.4.2.1. Objective Response Rate

RECIST-defined OR was determined by investigator overall tumor assessment and confirmed by the investigator at least 4 weeks following initial documentation of tumor response. A statistically significant difference in confirmed ORR favoring sunitinib treatment over placebo treatment was observed: 8 of 86 (9.3%, Table 24) subjects randomized to the sunitinib arm had a confirmed response (2 CRs and 6 PRs), and no subjects on placebo had a confirmed OR ( $P = 0.0066$  for the treatment difference). Among the 41 subjects randomized to sunitinib who were continuing treatment at the time the study was terminated, 6 had prior demonstration of response, and the other 35 were still in evaluation for response, including 5 patients enrolled too recently to have undergone disease evaluation on study; therefore, the true ORR may have been underestimated in this study. The re-estimated ORR based on algorithmic assessment also demonstrated an ORR of 9.3% (all PRs) in the sunitinib arm and 0% in the placebo arm.

**Table 24. Objective Responses in ITT Population – Phase III Study A6181111**

Efficacy Parameter	Phase III Study A6181111			
	Investigator Overall Tumor Assessment			
	Investigator Overall Tumor Assessment		Algorithmic Tumor Assessment	
	Sunitinib (N=86)	Placebo (N=85)	Sunitinib (N=86)	Placebo (N=85)
Best objective response [n (%)] <sup>a</sup>				
Complete response	2 (2.3)	0	0	0
Partial response	6 (7.0)	0	8 (9.3)	0
Stable disease	54 (62.8)	51 (60.0)	56 (65.1)	49 (57.6)
Progressive disease	12 (14.0)	23 (27.1)	9 (10.5)	21 (24.7)
Indeterminate/not evaluable	12 (14.0)	11 (12.9)	13 (15.1)	15 (17.6)
Missing	---	---	---	---
Objective response rate [% (95% exact CI)] <sup>a</sup>	9.3 (4.1, 17.5)	0 (0, 4.2)	9.3 (4.1, 17.5)	0 (0.0, 4.2)
<i>P</i> value <sup>b</sup>	0.0066		0.0066	
SD >90 days	46 (53.5)	44 (51.8)	47 (54.7)	44 (51.8)
SD >184 days	30 (34.9)	21 (24.7)	31 (36.0)	20 (23.5)

Abbreviations: N = number of subjects randomized; CI = confidence interval; SD = stable disease; NET = neuroendocrine tumors; ITT = intent to treat

<sup>a</sup> Using exact method based on binomial distribution

<sup>b</sup> From Fisher's exact test.

Source: CSR Study A6181111

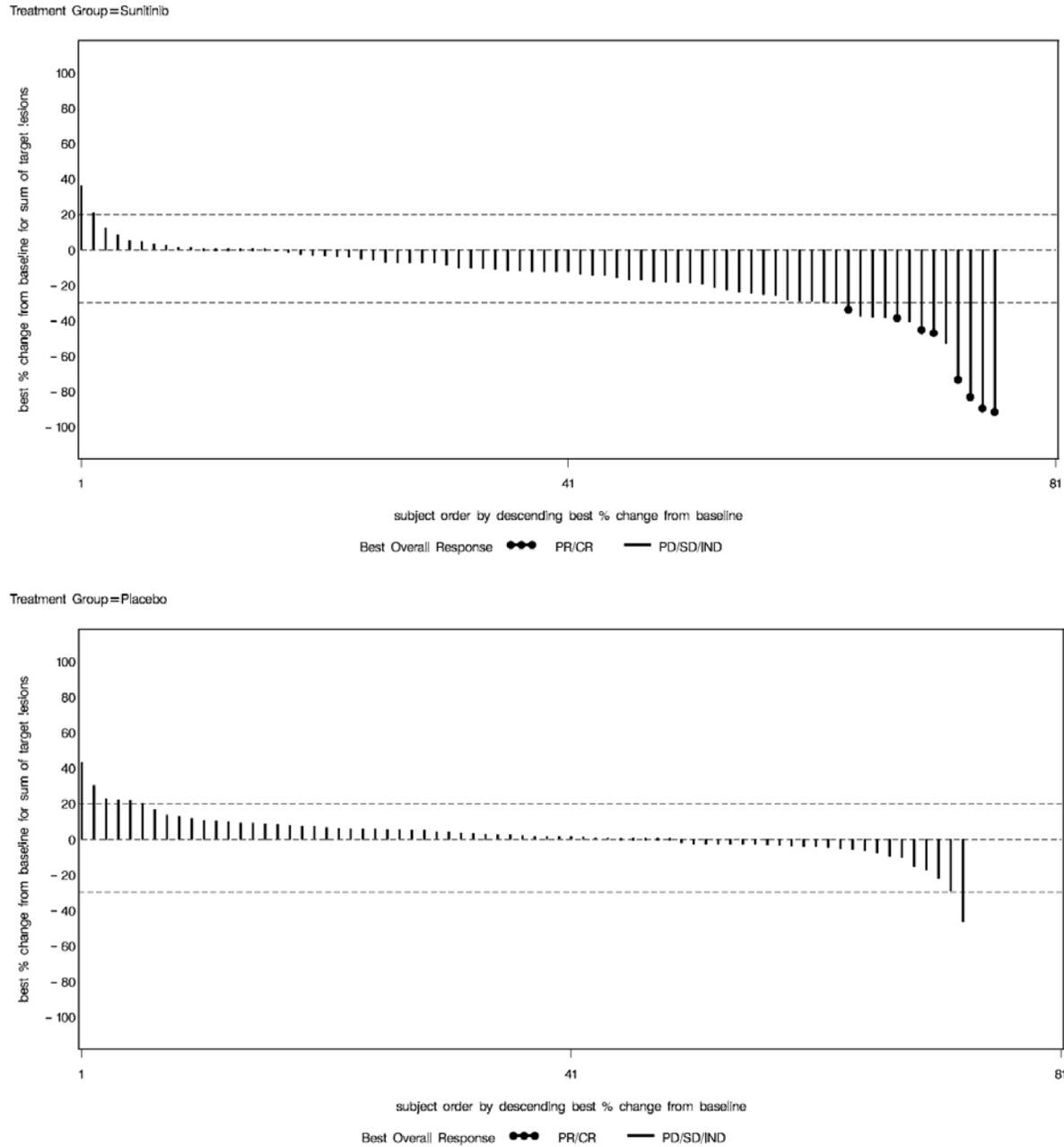
All subjects with a CR or PR in the IOTA analysis had a histological classification of nonfunctioning tumor, with the exception of 1 subject for whom the classification was unknown.

It should be noted that a number of sunitinib-treated subjects experienced reduction in the size of their target lesions but were classified as having 'stable disease' because changes in tumor size fell short of the lower limit of the RECIST-defined OR of -30%. In contrast, more than half of placebo-treated subjects who were classified as having stable disease actually had increases in target lesions, although below the lower limit of the RECIST-defined PD of +20% difference, as illustrated in Figure 11 below.

In the Algorithmic Assessment, two subjects (10241003 and 10311002) for whom CR was initially reported by investigator overall tumor assessments were assessed as having confirmed PRs. Subject 10241003 was a 56-year-old Asian female with non-functioning pancreatic NET with lesions in the pancreas and lymph node, who did not receive any prior systemic therapy or prior or concomitant somatostatin analogues. For assessment on 06 Feb 2009, a lesion in the head of the pancreas was reported as Too Small to Measure (TSTM) and a para-aortic lymph node was 10 mm. Assessment of tumor response based on reported tumor measurements indicated a 75% reduction in the sum of target lesions from baseline for this subject and a derived response of PR, while the investigator reported an overall tumor assessment and target lesion assessment of CR for this time point. In the subsequent tumor assessment on 03 Apr 2009 the lesion in the head of the pancreas and para-aortic lymph node were both assessed as TSTM. Re-analysis of the tumor lesion measurements based on algorithmic tumor data indicated an 83.3% reduction in the sum of target lesions from baseline for this subject and a derived response of PR (with imputation of 5 mm for lesions reported as TSTM), while the investigator reported an overall tumor assessment and target lesion assessment of CR for this time point.

Subject 10311002 was a 61-year-old white female with non-functioning pancreatic NET and lesions in the liver; she had previously received doxorubicin, streptozocin and lanreotide. For the assessment on 27 Mar 2008, 4 of 5 liver lesions were reported as 0 mm, while a fifth liver lesion was reported as TSTM. Assessment of tumor based on reported tumor measurements indicated a 91.7% reduction in the sum of target lesions from baseline for this subject and a derived response of PR (with imputation of 5 mm for the lesions reported as TSTM), while the investigator reported an overall tumor assessment and target lesion assessment of CR for this time point. In the subsequent tumor assessment on 23 May 2008, assessments of the 5 lesions were the same, and a 91.7% reduction in the sum of target lesions from baseline was again assessed for this subject along with a derived response of PR, while the investigator reported an overall tumor assessment and target lesion assessment of CR (confirmed CR) for this time point.

**Figure 11. Tumor Change from Baseline (%) for Target Lesions by Subject in ITT Population - Phase III Study A6181111**



Source: Summary of Clinical Efficacy

#### 4.3.4.2.2. Time to Tumor Response and Duration of Response

In the ITT population, the median TTR could not be estimated by Kaplan-Meier methods because relatively few sunitinib subjects (8/86) and no placebo subjects had a confirmed objective response (CR or PR). However, among the 8 subjects with OR, the arithmetic median TTR based on investigator assessment for the sunitinib arm was 3.1 months (range:

0.8 to 11.1 months). The re-estimation of the arithmetic median TTR based on algorithmic tumor data resulted in a 2.2 month median for the sunitinib arm (range: 0.8 to 5.6 months).

Among the 8 subjects treated with sunitinib who had an objective tumor response, only 1 subject experienced disease progression prior to termination of the study. The remaining 7 subjects continued with an ongoing tumor response 0.9+ to 15.0+ months following initial documentation of objective response until the study was terminated. With only 1 progression documented following objective response, median DR by investigator overall tumor assessment could not be estimated in this study using Kaplan-Meier methods, although the median exceeded 8 months based upon the durations at study completion. In the re-analysis based on algorithmic assessments, among the 8 subjects treated with sunitinib who had an objective tumor response, the durations of response were 1.8+, 2.8, 6.4+, 9.8+, 9.9, 10.9, 11.4+, and 13.1 months, with an arithmetic median of 9.9 months (range: 1.8 to 13.1 months, where “+” indicates that DR was ongoing at the time of study closure).

#### 4.3.4.2.3. Overall Survival

OS was analyzed based upon data from all subjects randomized in the study (ITT population). Dates of death recorded in Study A6181111 and the extension studies A6181114 and A6181078 occurring on or before the data cutoff date of 15 April 2009 were included in the analysis. Thirty deaths were reported among the 171 randomized subjects as of 15 April 2009 with fewer deaths on the sunitinib arm (9 subjects; 10.5%) than on the placebo arm (21 subjects; 24.7%). Substantial percentages of subjects on the sunitinib and placebo arms (87.2% vs. 71.8%, respectively) were censored in the OS analyses, as they were still in follow-up at the time of the data cutoff date. The observed hazard ratio for death was 0.409 (95% CI: 0.187 - 0.894;  $P = 0.0204$ ) in favor of treatment with sunitinib. The median follow-up was 10.2 and 11.1 months for the sunitinib and placebo arms, respectively. Because of the relatively high number of events censored in the analysis of OS, the median OS could not be accurately estimated for either treatment arm. Overall survival using Kaplan-Meier methods is presented in Figure 12. The probability of survival at 6 months was 92.6% (95% CI: 86.3% - 98.9%) for subjects treated with sunitinib and 85.2% (95% CI: 77.1% - 93.3%) for subjects who received placebo.

An updated analysis of OS was performed as a part of the 120-day safety update at the request of the FDA. The OS update used a data cutoff date of 01 December 2009. During the follow-up period of 7.5 months from 16 April 2009 through 01 December 2009, 21 additional deaths were reported among subjects who had either withdrawn from the Phase III Study A6181111 due to disease progression or enrolled in one of the two open-label sunitinib extension studies upon notification of closure of Study A6181111. In all, 51 deaths were reported among the 171 subjects randomized to the Phase III Study A6181111 as of 01 December 2009 with fewer deaths on the sunitinib arm (21 subjects; 24.4%) than on the placebo arm (30 subjects; 35.3%). A substantial percentage of subjects on the sunitinib and placebo arms (70.9% vs. 58.8%, respectively) were censored in the OS analyses, as they remained in follow-up at the time of the data cutoff date. The median OS was not reached for either treatment arm. Although more subjects randomized to placebo had crossed over to sunitinib at the time of the updated OS analysis, Kaplan-Meier analysis of OS continued to favor the sunitinib treatment arm with an observed hazard ratio for death of 0.594 (95% CI:

0.340 – 1.038;  $P = 0.0644$ ; Figure 13). The probability of survival at 6 months was 91.6% (95% CI: 85.7% - 97.6%) for subjects in the sunitinib arm and 84.0% (95% CI: 76.0% - 92.0%) for subjects in the placebo arm.

The analysis of OS was repeated with a data cutoff date of June 1, 2010. In this analysis, 73 deaths were reported, including 34 (39.5%) in the sunitinib arm and 39 (45.9%) in the placebo arm. There was a 6.1 month difference in the observed median survival, with a 30.5 month (95% CI: 20.6-NR) median OS in the sunitinib arm and a 24.4 month (95% CI: 16.3-NR) median OS in the placebo arm. The HR for OS was 0.737 (95% CI: 0.465-1.168;  $P = 0.1926$ ), and the Kaplan-Meier analysis for OS demonstrated a persistent separation of the survival curves, despite the potentially greater effect of crossover (Figure 14).

Even though the magnitude of the effect of sunitinib on survival had likely been confounded by a large proportion of subjects in the placebo arm receiving sunitinib upon crossover, including many subjects who crossed over at study termination in the absence of disease progression, the updated survival analysis continued to favor treatment with sunitinib. The potential for confounding of the OS analysis by the crossover from placebo to open-label sunitinib treatment was not explored.

**Table 25. Overall Survival as of 15 April 2009 in ITT Population – Phase III Study A6181111**

Efficacy Parameter	Phase III Study A6181111	
	Sunitinib (N=86)	Placebo (N=85)
Number of deaths [n (%)]	9 (10.5)	21 (24.7)
Subjects censored [n (%)] <sup>a</sup>	77 (89.5)	64 (75.3)
Reason for censorship [n (%)]		
In follow-up at data cutoff	75 (87.2)	61 (71.8)
Subject withdrew consent for additional follow-up	2 (2.3)	1 (1.2)
Lost to follow-up	0	2 (2.4)
Survival probability at 6 months <sup>b</sup> (95% CI) <sup>c</sup>	92.6 (86.3, 98.9)	85.2 (77.1, 93.3)
Hazard ratio (sunitinib vs. placebo) <sup>d</sup> (95% CI)	0.409 (0.187, 0.894)	
$P$ value <sup>e</sup>	0.0204	

Note: Information from open-label extension studies is included and kept under the original treatment arm  
Abbreviations: N = number of subjects; CI = confidence interval; NET = neuroendocrine tumors; NR = not reported; ITT = intent to treat

<sup>a</sup> Reasons for censoring in Study A6181111 included: subject in follow-up as of the data cutoff date (87.2% vs 71.8% for sunitinib vs placebo), consent withdrawn (2.3% vs 1.1%), and lost to follow-up (0% vs 2.4%)

<sup>b</sup> Estimated from the Kaplan-Meier curve

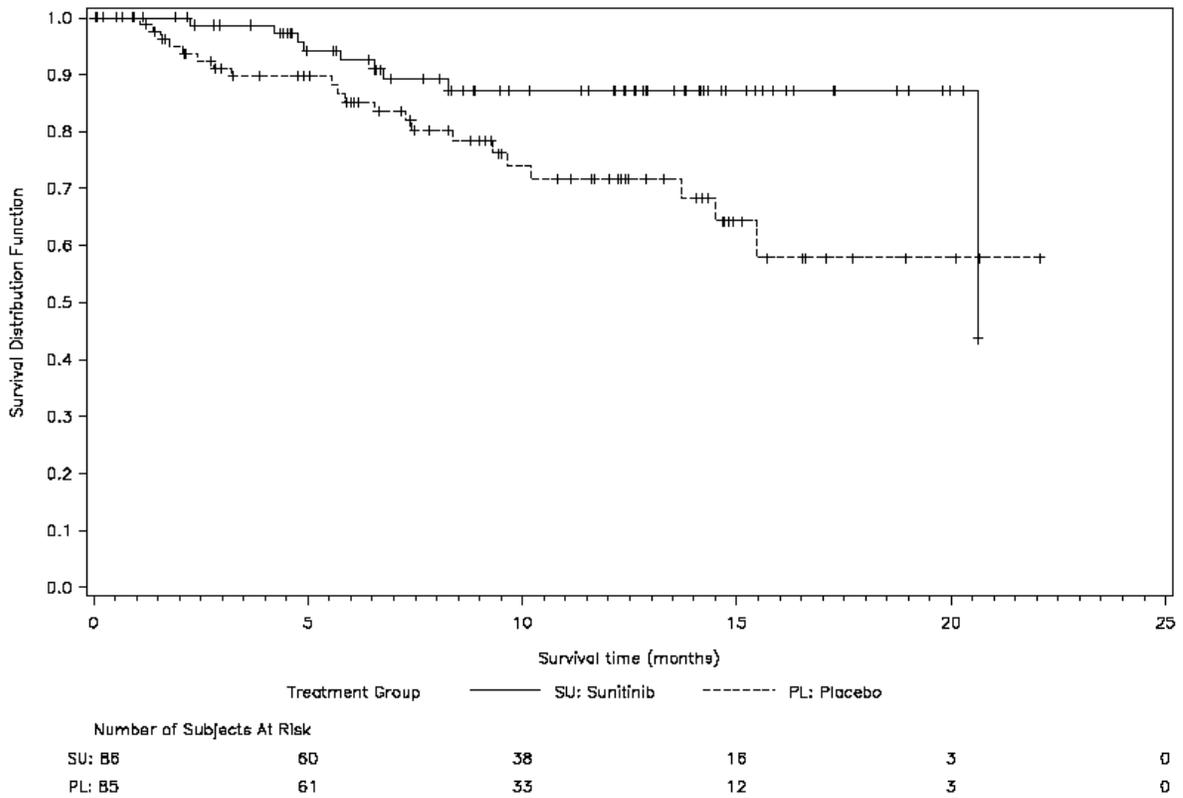
<sup>c</sup> Calculated from the product-limit method

<sup>d</sup> Based on the Cox proportional hazards model

<sup>e</sup> 2-sided  $P$  value from the unstratified log-rank test.

Source: CSR Study A6181111

**Figure 12. Kaplan-Meier Curves of Overall Survival as of 15 April 2009 in ITT Population – Phase III Study A6181111**



Source: CSR Study A6181111

Note: Data from the open-label extension studies is included and kept under the original treatment arm. For subjects known to be alive at the time the database was closed for analysis, survival data were censored on the date they were last known to be alive.

**Table 26. Summary of Overall Survival as of 01 December 2009 in ITT Population - Phase III Study A6181111**

	<b>Sunitinib N = 86</b>	<b>Placebo N = 85</b>
Number of deaths [n (%)]	21 (24.4)	30 (35.3)
Cause of death [n (%)]		
Disease under study	18 (20.9)	25 (29.4)
Study treatment toxicity	0	0
Unknown	0	0
Other	3 (3.5)	5 (5.9)
Subjects censored [n (%)]	65 (75.6)	55 (64.7)
Reason for censorship [n (%)]		
In follow-up at data cutoff	61 (70.9)	50 (58.8)
Subject withdrew consent for additional follow-up	3 (3.5)	2 (2.4)
Lost to follow-up	1 (1.2)	3 (3.5)
Survival probability at 6 months <sup>a</sup> (95% CI) <sup>b</sup>	91.6 (85.7, 97.6)	84.0 (76.0, 92.0)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI) <sup>c</sup>		
25%	18.9 (13.9, -)	9.3 (6.5, 15.5)
50%	-(21.5, -)	-(16.3, -)
75%	-	-
Hazard ratio (sunitinib vs. placebo) <sup>d</sup> (95% CI)	0.594 (0.340, 1.038)	
<i>P</i> value <sup>e</sup>	0.0644	

Note: All subjects who were originally randomized in Study A6181111 were included and were kept under the original randomized treatment arm.

Abbreviations: N = number of subjects; CI = confidence interval; ITT = intent to treat

<sup>a</sup> Estimated from the Kaplan-Meier curve

<sup>b</sup> Calculated from the product limit method

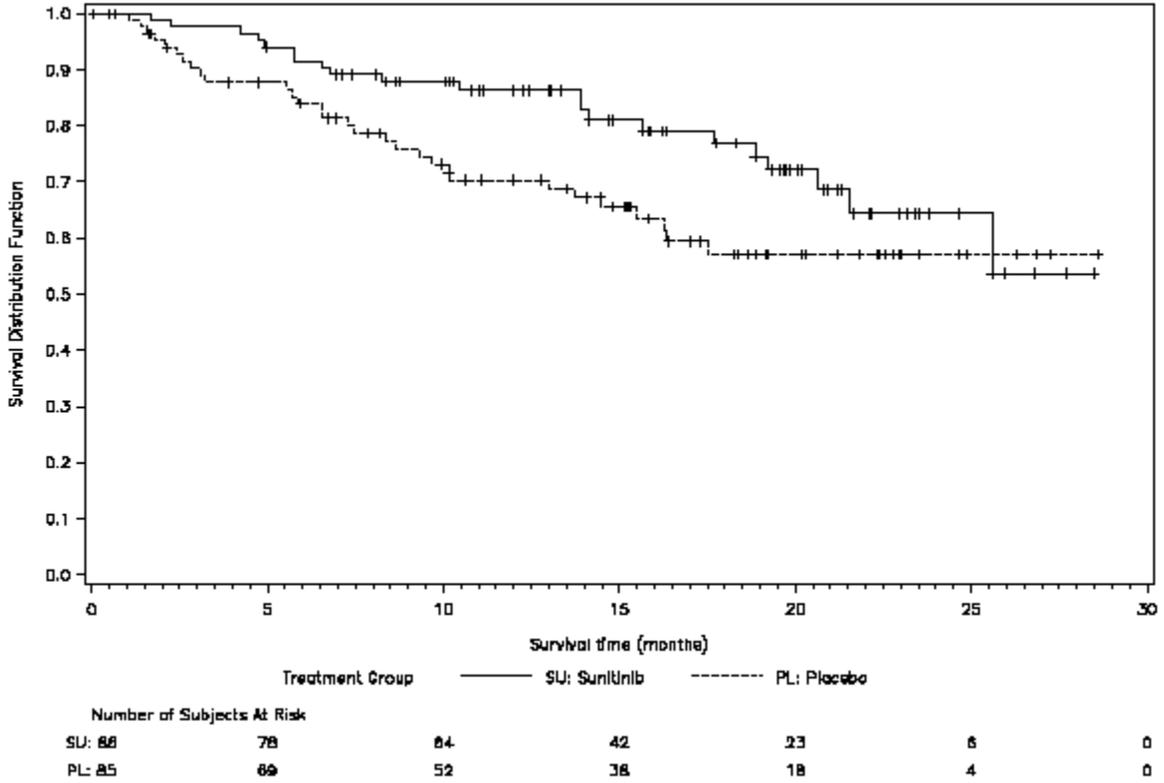
<sup>c</sup> Based on the Brookmeyer and Crowley method

<sup>d</sup> Based on the Cox proportional hazards model

<sup>e</sup> 2-sided *P* value from the unstratified log-rank test

Source: Summary of Clinical Efficacy

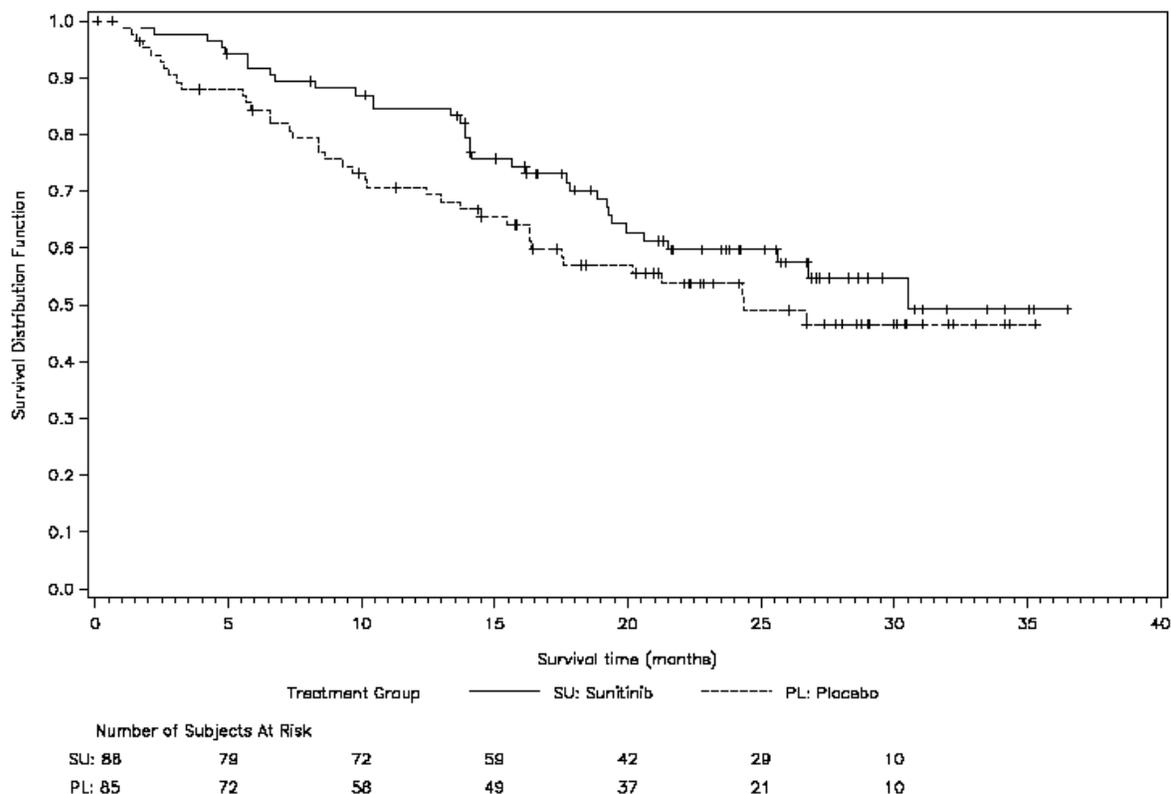
**Figure 13. Kaplan-Meier Curves of Overall Survival as of 01 December 2009 in ITT Population -Phase III Study A6181111**



Source: Summary of Clinical Efficacy

Note: All subjects who were originally randomized in Study A6181111 were included and were kept under the original randomized treatment arm.

**Figure 14. Kaplan-Meier Curves of Overall Survival as of 01 June 2010 in Intent-to-Treat Population – Phase III Study A6181111**



Source: Summary of Clinical Efficacy

### 4.3.4.3. Other Clinical Benefits

#### 4.3.4.3.1. Hormonal Levels and Tumor Marker Responses

Hormonal levels were collected from 6 subjects, 3 subjects randomized to placebo and 3 subjects randomized to sunitinib. Among these 6 subjects, only one subject had baseline information. This subject in the placebo arm had CgA levels that were normal at baseline and remained normal during the study. Two subjects (1 in each arm) with elevated gastrin levels approximately 2 weeks after randomization demonstrated increases 2 weeks later. One subject in the sunitinib arm had gradual increases in CgA levels from Day 30-464. Hormonal levels for the other 2 subjects remained relatively constant.

#### 4.3.4.3.2. Concomitant Medication Usage

Concomitant medication usage was evaluated across various histologic tumor subtypes to evaluate whether study treatment impacted specific concomitant drug usage among the various histologic subtypes. Initiation of somatostatin analog therapy was less common in subjects randomized to sunitinib versus placebo (1.2% vs. 8.2%, respectively). Additionally, one of 21 subjects (4.8%) on the sunitinib arm receiving a somatostatin analog at baseline

discontinued treatment with a somatostatin analog on study while none of 16 subjects on the placebo arm receiving a somatostatin analog at baseline discontinued treatment with a somatostatin analog on study.

Use of disease-specific concomitant medications was also evaluated for each functional histology. Use of medications for acid-related disorders, including proton pump inhibitors and H<sub>2</sub> antagonists, was evaluated among the 19 subjects with gastrinoma, although discontinuation of such medication would be unexpected even with disease improvement. All 9 subjects randomized to sunitinib and 9/10 subjects randomized to placebo took one or more concomitant medications for acid-related disorders during the study; one subject in the placebo arm switched from a proton pump inhibitor to another anti-acid medication. Use of glucose and glucagon was assessed among 4 subjects with insulinoma (2 in each treatment arm). None of these 4 subjects took these concomitant medications before randomization; however, 1 subject randomized to placebo started treatment with glucose on day 45 and received glucagon on day 46. Use of anti-diarrheal medications was evaluated among 2 subjects with VIPoma, both of whom were randomized to placebo. One subject received treatment with loperamide before study randomization and continued treatment during study, and the second subject received loperamide on Study days 1-3. Use of insulin was evaluated among 5 subjects with glucagonoma. Of the 3 subjects in the sunitinib arm, two were on insulin at study start, 1 of whom stopped insulin for over 120 days after study start; none of the 2 subjects in the placebo arm took insulin.

In summary, 27 subjects in the sunitinib treatment arm were taking one or more disease-specific concomitant medications at the time of randomization; 2 subjects stopped concomitant medication, and 1 subject started disease-specific concomitant medication on study (Table 27). In contrast, 21 subjects in the placebo arm were taking disease-specific concomitant medication at the time of randomization; none of them discontinued concomitant medication, and 7 subjects started a disease-specific concomitant medication during study. Thus, while few subjects in either arm were able to discontinue disease-specific concomitant medications, more subjects in the placebo arm started such medication on study.

**Table 27. Use of Disease-Specific Concomitant Medications - Phase III Study A6181111**

Histology	Number of Subjects							
	Sunitinib				Placebo			
	Histology	Conmed at Baseline <sup>a</sup>	Stopped Conmed	Started Conmed	Histology	Conmed at Baseline <sup>a</sup>	Stopped Conmed	Started Conmed
Insulinoma <sup>b</sup>	2	0	0	0	2	0	0	1
Gastinoma <sup>c</sup>	9	9	0	0	10	9	0	0
VIPoma <sup>d</sup>	0	0	0	0	2	1	0	1
Glucagonoma <sup>e</sup>	3	2	1	0	2	0	0	0
Subtotal <sup>f</sup>	14	11	1	0	16	10	0	2
Any (somatostatin analogue use) <sup>g</sup>	86	21	1	1	85	16	0	7
Total	86	27	2	1	85	21	0	7

Abbreviations: Conmed = concomitant medication

<sup>a</sup> Number with concomitant medication at baseline refers to the number of subjects with the specified histology who took concomitant medications specific for that histology as defined for each histologic type;

<sup>b</sup> Concomitant medications evaluated for insulinoma included glucagon and glucose;

<sup>c</sup> Concomitant medications evaluated for gastrinoma includes medications for acid-related disorders;

<sup>d</sup> Concomitant medications evaluated for VIPoma included loperamide, loperamide hydrochloride, and Lomotil;

<sup>e</sup> Concomitant medications evaluated for glucagonoma included insulin;

<sup>f</sup> Subtotal includes all histology subtypes except listed above this row;

<sup>g</sup> All subjects were evaluated for concomitant use of somatostatin analogs;

Source: CSR Study A6181111

#### 4.3.4.3.3. Patient-Reported Outcome Results

Patient-reported outcomes were assessed by EORTC QLQ-C30. There was no significant difference in global QoL for patients on sunitinib as compared to patients on placebo. In all five functional domains (cognitive, emotional, physical, role, and social functioning), the use of sunitinib did not have any clinically significant negative effect. Clinical significance was interpreted by a minimal important difference approach and defined as a difference of at least 10 points in a domain or scale in either direction while statistical significance was defined as  $P$  value < 0.05. The analyses also showed limited negative symptomatic effects for patients on the sunitinib arm. No clinically significant differences were noted in appetite loss, dyspnea, fatigue, financial difficulties, nausea and vomiting, and pain, between the two treatment groups. In comparing across arms, adverse symptomatic effects for patients on the sunitinib arm were limited to clinically and statistically significantly worsening of diarrhea at all assessment time points within the sunitinib arm. Subjects in the sunitinib arm also reported a statistically significant reduction in constipation as compared to subjects in the placebo arm at cycles 2, 3, and 4 and a statistically significant worsening of insomnia at cycles 2 through 7; however, these changes were not clinically significant. Taken together, these results suggested that overall global health-related QoL was maintained for patients on the sunitinib arm in comparison to placebo for this study, and that symptoms had limited impact on patient's global QoL and functioning scales.

#### 4.3.4.3.4. Comparison of Results in Demographic Subpopulations

The influence of demographic factors (race, age and gender) on the treatment effect was analyzed for the primary endpoint PFS. As shown in Table 28, the improvement in PFS was consistent across baseline factors of age, race, and gender.

**Table 28. Progression-Free Survival by Age, Gender and Race Based on Investigator Overall Tumor Assessment and Algorithmic Assessment in ITT Population – Phase III Study A6181111**

	Investigator Overall Tumor Assessment		Algorithmic Assessment	
	Sunitinib N=86	Placebo N=85	Sunitinib N=86	Placebo N=85
<b>Age</b>				
<b>&lt; 65 years, n</b>	64	62	64	62
Kaplan-Meier estimate of time to event				
Median PFS <sup>a</sup> (95% CI) (months)	11.1 (7.2, 19.8)	5.4 (3.4, 6.0)	8.3 (7.4, 13.6)	3.7 (3.4, 5.5)
Hazard ratio <sup>b</sup> (%) versus placebo (95% CI)	0.474 (0.284, 0.793)		0.473 (0.283, 0.789)	
<b>≥ 65 years, n</b>	22	23	22	23
Kaplan-Meier estimate of time to event				
Median PFS <sup>a</sup> (95% CI) (months)	* (6.0, *)	7.7 (5.7, 9.6)	* (12.7, *)	7.9 (5.7, 9.6)
Hazard ratio <sup>b</sup> (%) versus placebo (95% CI)	0.223 (0.071, 0.702)		0.100 (0.022, 0.463)	
<b>Race</b>				
<b>White, n</b>	48	53	48	53
Kaplan-Meier estimate of time to event				
Median PFS <sup>a</sup> (95% CI) (months)	11.4 (5.7, *)	7.4 (3.6, 8.4)	11.4 (6.0, 13.6)	7.9 (3.5, 9.6)
Hazard ratio <sup>b</sup> (%) versus placebo (95% CI)	0.487 (0.257, 0.923)		0.410 (0.203, 0.825)	
<b>Non-White, n</b>	38	32	38	32
Kaplan-Meier estimate of time to event				
Median PFS <sup>a</sup> (95% CI) (months)	19.8 (7.4, 19.8)	3.9 (1.8, 5.8)	12.7 (7.4, 19.7)	3.7 (1.8, 5.7)
Hazard ratio <sup>b</sup> (%) versus placebo (95% CI)	0.353 (0.179, 0.695)		0.374 (0.196, 0.715)	
<b>Gender</b>				
<b>Male, n</b>	42	40	42	40
Kaplan-Meier estimate of time to event				
Median PFS <sup>a</sup> (95% CI) (months)	11.1 (7.2, 19.8)	5.5 (3.6, 7.3)	8.3 (7.4, 16.9)	5.4 (3.6, 7.7)
Hazard ratio <sup>b</sup> (%) versus placebo (95% CI)	0.374 (0.200, 0.701)		0.450 (0.244, 0.830)	
<b>Female, n</b>	44	45	44	45
Kaplan-Meier estimate of time to event				
Median PFS <sup>a</sup> (95% CI) (months)	13.6 (6.1, 13.6)	6.0 (3.0, 10.9)	12.7 (11.4, 13.6)	3.7 (1.9, 7.9)
Hazard ratio <sup>b</sup> (%) versus placebo (95% CI)	0.477 (0.242, 0.939)		0.329 (0.159, 0.682)	

Abbreviations: N = number of subjects; n = number of subjects in group; CI = confidence interval; PFS = progression-free survival; ITT = intent to treat

<sup>a</sup> Based on the Brookmeyer and Crowley method;

<sup>b</sup> Based on the Cox proportional hazards model;

\* Not reached.

Source: CSR Study A6181111

### 4.3.5. Safety Results of Pivotal Phase III Study A6181111

#### 4.3.5.1. Treatment-Emergent, All-Causality Adverse Events

Nearly all subjects (sunitinib 82, 98.8%; placebo 78, 95.1%; Table 29) experienced treatment-emergent, all-causality AEs. AEs were most commonly associated with the Gastrointestinal disorders SOC (89.2% in sunitinib arm vs. 73.2% in placebo arm) or General disorders and administration site conditions SOC (80.7% of sunitinib subjects and 67.1% of placebo subjects).

The most common AEs (reported in  $\geq 5\%$  of subjects in the sunitinib arm, all causalities) are summarized in Table 29. The most common AEs, reported higher at least by 10 percentage points in the sunitinib arm as compared to the placebo arm, included diarrhea (59% vs. 39%), nausea (44.6% vs. 29.3%), hair color changes (28.9% vs. 1.2%), neutropenia (28.9% vs. 3.7%), hypertension (26.5% vs. 4.9%), palmar-plantar erythrodysesthesia syndrome (22.9% vs. 2.4%), stomatitis (21.7% vs. 2.4%), dysgeusia (20.5% vs. 4.9%), epistaxis (20.5% vs. 4.9%), rash (18.1% vs. 4.9%) and thrombocytopenia (16.9% vs. 4.9%). These differences were not adjusted for differences in duration of sunitinib or placebo treatment. None of the treatment-emergent, all-causality AEs was reported in  $\geq 10\%$  more subjects in the placebo arm as compared to the sunitinib arm.

Grade 3/4 AEs (all causalities) were more frequently experienced by subjects treated with sunitinib than those treated with placebo (49.4% vs. 43.9%). The most frequent grade 3/4 AEs (all causalities) were neutropenia (12% in sunitinib arm vs. 0 in placebo arm), hypertension (9.6% in sunitinib arm vs. 1.2% in placebo arm), leukopenia (6% in sunitinib arm vs. 0 in placebo arm), and palmar-plantar erythrodysesthesia syndrome (6% in sunitinib arm vs. 0 in placebo arm). Grade 3/4 abdominal pain and fatigue were more frequent in the placebo arm (9.8% and 8.5% of subjects, respectively) compared to the sunitinib arm (4.8% of subjects for each AE). Grade 3/4 abdominal pain upper was reported in 1 subject in the sunitinib arm only. Grade 3/4 diarrhea was reported for 4.8% of subjects in the sunitinib arm and 2.4% of subjects in the placebo arm, while grade 3/4 nausea was reported in 1.2% of subjects in each treatment arm. None of the AEs (all causalities) that were experienced by  $\geq 5\%$  of sunitinib-treated subjects was reported as a grade 5 AE.

**Table 29. Most Common (≥5% Sunitinib-Treated Subjects) Treatment-Emergent, All-Causality Adverse Events – Phase III Study A618111**

Number (%) of Subjects with Preferred Adverse Event Term*	Sunitinib (N=83)		Placebo (N=82)	
	All Grades	Grade 3/4 <sup>a</sup>	All Grades	Grade 3/4 <sup>a</sup>
Any AE	82 (98.8)	41 (49.4)	78 (95.1)	36 (43.9)
Diarrhea	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 erythrodysesthesia 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 oedema	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

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**Table 29. Most Common (≥5% Sunitinib-Treated Subjects) Treatment-Emergent, All-Causality Adverse Events – Phase III Study A6181111**

Chest pain	5 (6.0)	0	5 (6.1)	0
Decreased appetite	5 (6.0)	0	4 (4.9)	0
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

\*Common Terminology Criteria for Adverse Events (CTC AE) Version 3.0

Abbreviations: N = number of subjects; AEs = adverse events

<sup>a</sup>None of the AEs in this table was reported with a severity of grade 5.

Source: CSR Study A6181111

There were 4 (4.8%) and 6 (7.3%) subjects with grade 5 treatment-emergent, all-causality AEs in the sunitinib and placebo arms, respectively, with 3 subjects in each arm having a grade 5 AE of disease progression. In the sunitinib arm, these events were ascites, cardiac failure, and general physical health deterioration each experienced by 1 subject and disease progression experienced by 3 subjects. In the placebo arm, these events were renal failure acute and dehydration each experienced by 1 subject, general physical health deterioration and hepatic failure each experienced by 2 subjects, and disease progression experienced by 3 subjects. Deaths are discussed in Section 4.3.5.3.

Because the frequency of some events may have been underestimated by reliance on single AE PTs, some AEs were also summarized by the use of clustered AE PTs, including (1) fatigue and asthenia, (2) stomatitis, oral discomfort and related oral syndromes, (3) hypertension, and (4) hand-foot syndrome and related disorders. As shown in Table 30, these clustered AE PTs were more frequent in the sunitinib arm than in the placebo arm, both for treatment-emergent, all-causality AEs and treatment-related AEs. For the clustered terms ‘stomatitis, oral discomfort and related oral syndromes’, ‘hypertension’, and ‘hand-foot syndrome and related skin disorders’, 6-10% of subjects in the sunitinib arm experienced grade 3/4 treatment-related AEs compared to no subjects in the placebo arm. For the clustered term ‘fatigue/asthenia’, the frequency of grade 3/4 treatment-related AEs was similar for both arms (7% in sunitinib arm vs. 6% in placebo arm).

Most subjects experienced clustered AE PTs with a maximum severity of grade 1 or 2. There were no subjects with clustered AE PTs of grade 5 maximum severity in either treatment arm. One subject (in the sunitinib arm) experienced treatment-related fatigue/asthenia of grade 4 maximum severity.

**Table 30. Frequency of Selected Clustered Adverse Event Preferred Terms – Phase III Study A6181111**

Number (%) of Subjects with Clustered Term	Sunitinib (N=83)		Placebo (N=82)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
<b>All Causalities</b>				
Fatigue/Asthenia <sup>a</sup>	50 (60.2)	7 (8.4)	43 (52.4)	10 (12.2)
Stomatitis, Oral discomfort and related oral syndromes <sup>b</sup>	40 (48.2)	5 (6.0)	15 (18.3)	0
Hypertension <sup>c</sup>	22 (26.5)	8 (9.6)	4 (4.9)	1 (1.2)
Hand-foot syndrome and related skin disorders <sup>d</sup>	19 (22.9)	5 (6.0)	2 (2.4)	0
<b>Treatment-Related</b>				
Fatigue/Asthenia <sup>a</sup>	46 (55.4)	6 (7.2)	32 (39.0)	5 (6.1)
Stomatitis, Oral discomfort and related oral syndromes <sup>b</sup>	40 (48.2)	5 (6.0)	14 (17.1)	0
Hypertension <sup>c</sup>	19 (22.9)	8 (9.6)	3 (3.7)	0
Hand-foot syndrome and related skin disorders <sup>d</sup>	19 (22.9)	5 (6.0)	2 (2.4)	0

Abbreviations: N = number of subjects

<sup>a</sup> Fatigue and Asthenia;

<sup>b</sup> Aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, gum ulceration, mouth ulceration, oral discomfort, oral mucosal blistering, oral pain, stomatitis, swollen tongue, tongue blistering, tongue oedema, tongue ulceration, mucosal dryness, mucosal inflammation, gingival ulceration, dry mouth, oropharyngeal blistering and mouth ulceration;

<sup>c</sup> Accelerated hypertension, essential hypertension, hypertensive crisis, diastolic hypertension, malignant hypertension, renovascular hypertension, systolic hypertension, labile hypertension, orthostatic hypertension, secondary hypertension;

<sup>d</sup> Palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema.

Source: CSR Study A6181111

Blood pressure measurements relevant to hypertension are discussed in Section 4.3.5.8.1.

#### 4.3.5.2. Treatment-Related Adverse Events

Treatment-related AEs were most commonly associated with the Gastrointestinal disorders SOC, General disorders and administration site conditions SOC, or skin and subcutaneous tissue disorders. Differences in AE frequencies between the sunitinib and placebo arms were not adjusted for differences in duration of sunitinib or placebo treatment.

The most common treatment-related AEs (those reported in  $\geq 5\%$  of subjects in the sunitinib arm) were diarrhea and nausea. For each of these treatment-related AEs, the incidence was greater for the sunitinib arm compared to the placebo arm: 53.0% and 38.6% of sunitinib subjects experienced treatment-related diarrhea and nausea, respectively, compared to 30.5% and 22.0% of placebo subjects. Other treatment-related AEs that were reported in  $\geq 10$  percentage points more subjects in the sunitinib arm compared to the placebo arm included: hair color changes (28.9% vs. 1.2%), neutropenia (28.9% vs. 3.7%), fatigue (28.9% vs. 17.1%), hypertension (22.9% vs. 3.7%), palmar-plantar erythrodysesthesia syndrome (22.9% vs. 2.4%), stomatitis (21.7% vs. 2.4%), dysgeusia (19.3% vs. 3.7%), epistaxis (19.3%

vs. 2.4%), thrombocytopenia (16.9% vs. 4.9%), rash (15.7% vs. 4.9%) and dyspepsia (14.5% vs. 1.2%). Only dyspnea was reported with greater frequency for the placebo arm compared to the sunitinib arm (9.8% vs. 7.2%). None of the treatment-related AEs was reported in  $\geq 10$  percentage points more subjects in the placebo arm compared to the sunitinib arm. None of these common AEs was reported with Grade 5 severity.

Treatment-related grade 3/4 AEs were more frequently experienced by sunitinib subjects (43.4%) than by placebo subjects (19.5%). The most frequent treatment-related grade 3/4 AEs were neutropenia (experienced by 12.0% of sunitinib subjects but by no placebo subjects), hypertension (9.6% of sunitinib but no placebo subjects), leukopenia (6.0% of sunitinib subjects but no placebo subjects) and palmar-plantar erythrodysesthesia syndrome (6.0% of sunitinib subjects but no placebo subjects).

**Table 31. Most Common (≥5% Sunitinib-Treated Subjects) Treatment-Related Adverse Events by Maximum CTCAE Severity – Phase III Study A6181111**

Number (%) of Subjects with Preferred Adverse Event Term	Sunitinib (N=83)		Placebo (N=82)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE	81 (97.6)	36 (43.4)	64 (78.0)	16 (19.5)
Diarrhea	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 erythrodysesthesia 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

Abbreviation: N = number of subjects

Note: Common Terminology Criteria for Adverse Events (CTC AE) Version 3.0

Source: CSR Study A6181111

One (1.2%) subject in each arm experienced grade 5 treatment-related AEs. The grade 5 events were cardiac failure in the sunitinib arm and dehydration in the placebo arm. On-study deaths are also discussed in Section 4.3.5.3.

Blood pressure measurements relevant to hypertension are discussed in Section 4.3.5.8.1.

#### 4.3.5.3. Deaths

Deaths are summarized in Table 32 for the As-Treated population. The incidence of death was higher for the placebo arm (21/82, 25.6%) compared to the sunitinib arm (9/83, 10.8%). The most common cause of death was “Disease under Study” in both the sunitinib and placebo treatment arms during both the on-treatment [4 (4.8%) sunitinib; 7 (8.5%) placebo] and follow-up [3 (3.6%) sunitinib; 12 (14.6%) placebo] periods of the study. Two deaths occurred as the result of AEs (heart failure on the sunitinib arm and dehydration on the placebo arm) that were considered related to study treatment.

**Table 32. Summary of Deaths – Phase III Study A6181111**

Cause of Death	Sunitinib N = 83	Placebo N = 82
Deaths	9 (10.8)	21 (25.6)
Subjects who Died while On Study <sup>a</sup>	5 (6.0)	9 (11.0)
Disease under study	4 (4.8)	7 (8.5)
Study treatment toxicity	1 (1.2) <sup>bc</sup>	1 (1.2) <sup>cd</sup>
Other	0	1 (1.2) <sup>e</sup>
Subjects who Died during Follow-up <sup>f</sup>	4 (4.8)	12 (14.6)
Disease under study	3 (3.6)	12 (14.6)
Study treatment toxicity	0	0
Other	1 (1.2) <sup>g</sup>	0

Note: Deaths of subjects during extension Studies A6181078 and A6181114 are also included.

Abbreviations: N = number of subjects

<sup>a</sup> On-study deaths are those that occurred after the first dose of study drug and within 28 days of the last dose of study drug;

<sup>b</sup> Heart failure (Subject 10061002);

<sup>c</sup> Reason for death was presented as ‘other’;

<sup>d</sup> Dehydration (Subject 10311006);

<sup>e</sup> Hepatic failure (Subject 10351002);

<sup>f</sup> Follow-up deaths are those that occurred more than 28 days after the last dose of study medication;

<sup>g</sup> Cardiac insufficiency (Subject 10491001).

Source: CSR Study A6181111

Subjects who experienced a grade 5 AE during the Phase III Study A6181111 are presented in Table 33. With the exception of grade 5 AEs of cardiac failure (1 sunitinib subject) and dehydration (1 placebo subject) that were considered to be treatment-related, these AEs were considered to be due to the disease under study.

**Table 33. Subjects with Treatment-Emergent Grade 5 Adverse Events – Phase III Study A6181111**

Subject Number	Sex/ Age	Preferred Term	Start/ Stop Day	Causality
<b>Sunitinib (N=83)</b>				
10031001	M/52	Disease progression	603/>603	Disease under study
10421007	M/39	Disease progression	122/>145	Disease under study
10531002	F/54	General physical health deterioration	115/>145	Disease under study
		Ascites	89/>115	Disease under study
10661002	F/63	Disease progression	89/127	Disease under study
		Cardiac failure	68/68	Study drug
<b>Placebo (N=82)</b>				
10291001	F/60	Disease progression	41/63	Disease under study
10311006	F/78	Dehydration	29/>29	Study drug
10331003	M/44	Disease progression	48/>48	Disease under study
10351002	M/58	Hepatic failure	173/175	Disease under study
10401001	F/44	General physical health deterioration	39/>40	Disease under study
		Hepatic failure	39/>39	Disease under study
		Renal failure acute	39/>39	Disease under study
10421009	M/76	Disease progression <sup>a</sup>	233/>233	Disease under study
		General physical health deterioration	226/>283	Disease under study

Abbreviations: N = number of subjects

<sup>a</sup> Not reported as a serious adverse event; Use of '>' represents imputed data.

Source: CSR Study A6181111

Subject 10661002, a 63-year-old female on the sunitinib arm, died of cardiac failure. The subject had a primary diagnosis of malignant neoplasm of islets of Langerhans (histological classification: non-functioning), duration since first diagnosis 0.62 years. The subject was treated with sunitinib 37.5 mg on a CDD schedule from 15 November 2007 to 20 January 2008. There were no dose modifications or interruptions prior to hospitalization. She was hospitalized on (b) (6) for hyperkalemia, kidney deficiency, liver dysfunction, heart failure, and ventricular arrhythmia. During the hospitalization, the subject had gastrointestinal tract hemorrhage. The events hyperkalemia, hepatic function abnormal, and ventricular arrhythmia were considered as life-threatening. The subject died on (b) (6) due to heart failure. Laboratory investigations performed on 21 January 2008 revealed blood potassium levels of 7.5 mmol/L (normal range 3.6-5.0 mmol/L), blood creatinine of 351 µmol/L (normal range 44-80 µmol/L), AST 11857 U/L (normal range 2-35 U/L), ALT 6099 U/L (normal range 2-50 U/L), PT at 20% (normal range 70%-100%). An ECG that day revealed a QTc interval prolongation (see Section 4.3.5.8.3). The investigator considered that the cardiac failure was treatment-related.

Subject 10311006, a 79-year-old female on the placebo arm, died of dehydration. The subject had a primary diagnosis of malignant neoplasm of islets of Langerhans (histological classification: gastrinoma), duration since first diagnosis 1.78 years. This subject had a medical history of diarrhea since 2006, linked to primary diagnosis, grade 2 on 20 September 2008. The subject was suffering from dehydration since 23 September 2008; metoclopramide was prescribed on this date because of vomiting. Study drug had been stopped on 20 September 2008 due to a non-serious AE of diarrhea grade 2, and the subject

was permanently discontinued due to dehydration. The subject was admitted to the hospital on (b) (6) with inflammatory syndrome, renal failure, predominant abdominal and peri-umbilical pain. She had received treatment with intravenous fluids on that date, and laboratory tests were performed. An abdominal spiral CT scan (without contrast agent because of the renal insufficiency) was also performed and showed a major hepatomegaly with numerous metastatic lesions in both left and right liver, a major pancreas tumor, and an important fat mass around the tumor. This mass pushed on the duodenum, at the junction between the second and the third duodenum, and was responsible for a gastric liquid stasis. No ascites, perforation or abscess, or occlusive syndrome was noted. On (b) (6), the subject died due to dehydration. The investigator considered there was a reasonable possibility that the dehydration was treatment-related (treatment was blinded).

#### 4.3.5.4. Other Serious Adverse Events

##### 4.3.5.4.1. Frequency of Treatment-Emergent All-Causality Serious Adverse Events

All-causality SAEs were more commonly reported in subjects receiving placebo (41.5%; Table 34) compared to sunitinib (26.5%). Treatment-emergent, all-causality SAE were most frequently reported for the Gastrointestinal disorders SOC and the General disorders and administration site conditions SOC. The most common treatment-emergent, all-causality SAEs for sunitinib-treated subjects (experienced by at least 2% of the subjects) were disease progression (3 subjects, 3.6%) and abdominal pain, abdominal pain upper, cardiac failure, nausea, renal failure, and vomiting (2 subjects each, 2.4%). The most common treatment-emergent, all-causality SAEs for placebo-treated subjects were abdominal pain (4 subjects, 4.9%), vomiting (3 subjects, 3.7%), and disease progression (2 subjects, 2.4%), and nausea (1 subject, 1.2%).

**Table 34. Most Common (≥2% Sunitinib-Treated Subjects) Treatment-Emergent, All-Causality Serious Adverse Events – Phase III Study A6181111**

Preferred Term	Subjects n (%)	
	Sunitinib (N=83)	Placebo (N=82)
Any serious adverse event	22 (26.5)	34 (41.5)
Disease progression	3 (3.6)	2 (2.4)
Abdominal pain	2 (2.4)	4 (4.9)
Abdominal pain upper	2 (2.4)	0
Cardiac failure	2 (2.4)	0
Nausea	2 (2.4)	1 (1.2)
Renal failure	2 (2.4)	0
Vomiting	2 (2.4)	3 (3.7)

Abbreviation: N = number of subjects  
 Source: CSR Study A6181111

##### 4.3.5.4.2. Frequency of Treatment-Related Serious Adverse Events

Treatment-related SAEs were more commonly reported in subjects receiving sunitinib (13.3%) compared to placebo (7.3%), and these were most frequently gastrointestinal

disorders (6.0% of sunitinib subjects and 1.2% of placebo subjects). In sunitinib arm, abdominal pain upper, nausea, and renal failure were each experienced by 2 subjects (2.4%). The remaining events were limited to single occurrences. In the placebo arm, treatment-related SAEs were limited to single occurrences of abdominal pain, pyrexia, pneumonia, dehydration, back pain, pleurisy, pulmonary embolism, deep vein thrombosis, and hypoglycemia. Treatment-related SAEs are listed in Table 35.

**Table 35. Treatment-Related Serious Adverse Events – Phase III Study A6181111**

Subject Number	Sex/ Age	Preferred Term	Start/Stop Day	Grade	Outcome
Sunitinib (N=83)					
10131001	F/77	Mucosal inflammation	31/46	3	Resolved
		Anal abscess	31/66	3	Resolved
10151001	F/33	Diarrhea	17/22	2	Resolved
		Bile duct obstruction	16/31	2	Resolved
10231002	F/73	Leukopenia	27/61	3	Resolved
		Neutropenia	27/38	4	Resolved
		Thrombocytopenia	27/50	4	Resolved
		Cerebral hematoma	34/68	2	Resolved
10271002	M/46	Abdominal pain upper	159/167	1	Resolved
		Mallory-Weiss syndrome	54/57	3	Resolved
		Nausea	61/63	2	Resolved
		Nausea	165/167	3	Resolved
		Nausea	200/212	3	Resolved
		Vomiting	61/63	2	Resolved
		Vomiting	165/167	2	Resolved
		Vomiting	200/212	2	Resolved
10411003	M/58	Hypertension	31/41	3	Resolved
10421002	M/65	Renal failure	475/>475	2	Still present
10481006	F/64	Duodenal ulcer	5/21	3	Resolved
		Leukoencephalopathy	28/224	3	Resolved
10491001	M/75	Dyspnea	35/43	2	Resolved
		Dyspnea	68/85	2	Resolved
		Hemoptysis	35/37	2	Resolved
10661002	F/63	Cardiac failure	68/68	5	Fatal <sup>a</sup>
		Ventricular arrhythmia	68/68	4	Resolved
		Hepatic function abnormal	68/68	4	Resolved
		Hyperkalemia	68/68	4	Resolved
		Renal failure	68/68	4	Resolved
10661013	F/42	Abdominal pain upper	51/55	3	Resolved
		Abdominal pain	10/20	3	Resolved
10711002	F/66	Nausea	3/29	2	Resolved
		Fatigue	3/55	3	Resolved
Placebo (N=82)					
10091004	F/63	Hypoglycemia	177/182	2	Resolved
10091005	F/72	Pleurisy	33/38	2	Resolved
10231003	F/67	Pneumonia	107/118	3	Resolved
10311006	F/78	Dehydration	29/>29	5	Fatal <sup>b</sup>
10421006	F/39	Pyrexia	127/168	1	Resolved
		Back pain	114/168	2	Resolved
10661005	F/48	Abdominal pain	129/131	3	Resolved
		Pulmonary embolism	77/113	4	Resolved
		Deep vein thrombosis	77/113	2	Resolved

Abbreviations: N = number of subjects; M = male; F = female; Use of '>' represents imputed data  
Source: CSR Study A6181111

#### **4.3.5.5. Other Significant Adverse Events**

##### **4.3.5.5.1. Adverse Events Associated with Permanent Discontinuation**

Eighteen (21.7%) subjects and 14 (17.1%) subjects in the sunitinib and placebo arms, respectively, experienced AEs for which they were permanently discontinued from the study. The most common SOC of AEs leading to discontinuation was General disorders and administration site conditions (13 subjects). For 20 subjects [10 (12%) subjects in each arm], the AE leading to discontinuation was an SAE.

Subjects discontinuing due to AEs are listed in Table 36. In the sunitinib arm, the most common causality for AEs leading to discontinuation was study drug (10 subjects, 12%) compared to 2 subjects (2.4%) in the placebo arm. In the placebo arm, the most common causality for AEs was the disease under study. Seven (8.4%) sunitinib-treated subjects and 13 (15.9%) placebo-treated subjects were discontinued because of AEs that were related to the disease under study (pancreatic NET). Three (3.6%) sunitinib-treated subjects and 1 (1.2%) placebo-treated subject were discontinued due to other AEs.

**Table 36. Discontinuations Due to Adverse Events – Phase III Study A6181111**

Subject Number	Sex/ Age	Preferred Term	Start/Stop Day	Grade	Causality
<b>Sunitinib (N=83)</b>					
10031001	M/52	Disease progression <sup>a</sup>	603/>603	5	Disease under study
10031007	F/67	Spinal compression fracture <sup>a</sup>	141/146	NR	Other illness
10091001	F/42	Hyperbilirubinemia	141/>141	2	Disease under study
10091009	F/53	Fatigue	10/29	1	Study drug
10131001	F/77	Mucosal inflammation <sup>a</sup>	31/46	3	Study drug
10151001	F/33	Diarrhea <sup>a</sup>	17/22	2	Study drug
		Bile duct obstruction <sup>a</sup>	16/31	2	Study drug
		Catheter related infection <sup>a</sup>	15/23	1	Unknown
10171001	M/40	Hepatic encephalopathy <sup>a</sup>	250/>250	4	Disease under study
10191002	M/77	Asthenia	21/25	3	Study drug
10411002	F/56	Cardiomyopathy	41/>41	2	Study drug
		Hypertension	29/125	3	Study drug
10421007	M/39	Disease progression <sup>a</sup>	122/>145	5	Disease under study
10481006	F/64	Leukoencephalopathy <sup>a</sup>	28/224	3	Study drug
10491001	M/75	Cardiac failure <sup>a</sup>	77/>77	3	Valvular aortic stenosis
10531002	F/54	Ascites <sup>a</sup>	89/>115	5	Disease under study
		Disease progression <sup>a</sup>	89/127	5	Disease under study
10661001	F/49	Fatigue	204/219	2	Disease under study
10661002	F/63	Cardiac failure <sup>a</sup>	68/68	5	Study drug
10661013	F/42	Diarrhea	225/239	2	Study drug
10711002	F/66	Fatigue	100/133	4	Study drug
10721002	F/53	Neutropenia	124/139	3	Study drug
<b>Placebo (N=82)</b>					
10011001	M/65	Abdominal pain <sup>a</sup>	82/>85	3	Disease under study
10091004	F/63	Tremor	280/>288	1	Disease under study
10091008	M/60	Malignant pleural effusion <sup>a</sup>	4/>4	2	Disease under study
10191001	F/38	General physical health deterioration	144/>144	2	Disease under study
		Convulsion <sup>a</sup>	137/>143	3	Disease under study
10291001	F/60	Disease progression <sup>a</sup>	41/63	5	Disease under study
10311006	F/78	Dehydration <sup>a</sup>	29/>29	5	Study drug
10331003	M/44	Disease progression <sup>a</sup>	48/>48	5	Disease under study
10351002	M/58	Hepatic failure <sup>a</sup>	173/175	5	Disease under study
10401001	F/44	Hepatic failure <sup>a</sup>	39/>39	5	Disease under study
10421009	M/76	Disease progression	233/>233	5	Disease under study
10481001	F/57	Cerebrovascular accident <sup>a</sup>	49/52	3	Diabetes
10661005	F/48	Abdominal pain	242/252	3	Study drug
10661007	M/64	Fatigue	30/>37	3	Disease under study
10671004	F/55	Nausea <sup>a</sup>	73/81	3	Disease under study
		Vomiting <sup>a</sup>	73/81	3	Disease under study

Note: For Grade 5 AEs, the date of death may have been recorded as the date of resolution for the AE.

Abbreviations: N = number of subjects; M = male; F = female; NR = not reported; Use of '>' represents imputed data; <sup>a</sup> SAE

Source: Study A6181111 CSR

#### **4.3.5.5.2. Adverse Events Associated with Temporary Discontinuations or Dose Reductions**

Forty-five (54.2%) sunitinib-treated subjects and 27 (32.9%) placebo-treated subjects experienced treatment-emergent, all-causality AEs leading to temporary discontinuations or dose reductions. The most marked differences between the treatment arms were noted for the Blood and lymphatic system disorders SOC (14.5% and 0% of subjects in the sunitinib and placebo arms, respectively) and Skin and subcutaneous tissue disorders SOC (13.3% and 1.2%, respectively). In both treatment arms, AEs most commonly reported as leading to temporary discontinuations or dose reductions were in the Gastrointestinal disorders SOC [19 (22.9%) and 12 (14.6%) subjects in the sunitinib and placebo arms, respectively].

Treatment-related AEs leading to temporary discontinuations or dose reductions were reported in 39/83 (47%) subjects and 16/82 (19.5%) subjects in the sunitinib and placebo arms, respectively. The most marked differences between the treatment arms were noted for the Blood and lymphatic system disorders SOC (14.5% and 0% of subjects in the sunitinib and placebo arms, respectively), Gastrointestinal disorders SOC (21.7% and 4.9%, respectively), and Skin and subcutaneous tissue disorders SOC (13.3% and 1.2%, respectively). In the sunitinib arm, Gastrointestinal disorders were the most common SOC of AE leading to temporary discontinuation (21.7%). The most frequently reported individual treatment-related AEs resulting in temporary discontinuation or dose reduction for the sunitinib arm were neutropenia [10 (12.0%)], asthenia and diarrhea [7 (8.4%) each], thrombocytopenia and stomatitis [5 (6.0%) each], and nausea [4 (4.8%)].

#### **4.3.5.6. Analysis of Adverse Events by Organ System or Syndrome**

##### **4.3.5.6.1. Cardiac Dysfunction**

AEs indicative of cardiac dysfunction (e.g., PTs in the Cardiac Disorders SOC such as Cardiac failure, Cardiomyopathy, Congestive heart failure, Ventricular failure/dysfunction, and Ejection fraction decreased) and, where reported, measurements of cardiac function are reviewed in this section. Measurements of cardiac function were performed at screening or if clinically indicated.

Cardiac failure was reported as an AE in 2 subjects, both in the sunitinib arm and no subjects on the placebo arm: 1 subject had an AE of grade 3 Cardiac failure associated with a decline in LVEF from 60% to 37% that was not considered related to treatment. The second subject experienced grade 5 treatment-related cardiac failure. Cardiomyopathy was reported as an AE in 1 subject in the sunitinib arm and no subjects on the placebo arm. This AE, which was grade 2 in severity, was considered to be related to study treatment.

##### **4.3.5.6.2. Thyroid Dysfunction**

AEs indicative of thyroid dysfunction, including hyperthyroidism, hypothyroidism, thyroiditis, and blood TSH increased, are reported in this section. Overall, a few subjects had an AE indicative of thyroid dysfunction. Most of the AEs that were reported were considered to be related to treatment, and most had a severity of grade 1 or 2.

Hyperthyroidism was reported as an AE in 2 subjects on the placebo arm, and hypothyroidism was reported as an AE in 6 subjects on the sunitinib arm and 1 subject on the placebo arm. All but 1 of these events were considered to be treatment-related, and all of these events were grade 1 or 2 in severity and non-serious.

No cases of thyroiditis were reported.

Blood TSH increased was reported as an AE for 3 subjects in the sunitinib arm and no subjects in the placebo arm. All of these events were considered related to treatment and were grade 1 or 2 in severity.

No cases of grade 3, 4, or 5 thyroid dysfunction were reported as an AE in this study.

#### **4.3.5.6.3. Hemorrhagic Events**

Since the frequency of hemorrhagic AEs may have been underestimated by using only the PT Hemorrhage, hemorrhagic events were summarized as “bleeding complications” consisting of a cluster of AE PTs including the words hemorrhage, hematoma, or bleeding, and the following PTs: melaena, hematochezia, hematemesis, metrorrhagia, and hemoptysis. Epistaxis was not included in “bleeding complications”, as it was commonly reported.

All-causality “bleeding complications” were reported for 18 (21.7%) subjects in the sunitinib arm and 8 (9.8%) of subjects in the placebo arm. All of the events in the sunitinib arm were grade 1 or 2 in severity and 3/8 events in the placebo arm were grade 3 or 4 in severity; there were no grade 5 events. Treatment-related “bleeding complications” were reported for 16 (19.3%) subjects in the sunitinib arm and 3 (3.7%) subjects in the placebo arm. All treatment-related AEs of bleeding complications in both treatment arms were grade 1 or 2 in severity. Epistaxis was reported for 17 (20.5%) subjects in the sunitinib arm and 4 (4.9%) subjects in the placebo arm. All of the events were grade 1 or 2 in severity with the exception of 1 grade 3 case that was reported on the sunitinib arm. Most of the events were considered related to study treatment.

No cases of grade 5 “bleeding complications” or epistaxis were reported in this study.

#### **4.3.5.6.4. Thromboembolic Events**

Thromboembolic events were summarized as using a clustered term “arteriovenous thromboembolic events” consisting of the following cluster of AE PTs: deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, and thrombosis. Treatment-emergent, all-causality “arteriovenous thromboembolic events” were reported for 1 (1.2%) subject in the sunitinib arm and 5 (6.1%) subjects in the placebo arm. The event in the sunitinib arm was grade 2 in severity and 4/5 AEs in the placebo arm were grade 3/4 in severity; there were no grade 5 events. Treatment-related “arteriovenous thromboembolic events” were reported for no subjects in the sunitinib arm and 1 (1.2%) subject in the placebo arm. The treatment-related AE of “arteriovenous thromboembolic events” in the placebo arm was grade 3/4 in severity.

#### 4.3.5.6.5. Hypoglycemia

Treatment-emergent, all-causality hypoglycemia was reported as an AE for 8 (9.6%) subjects and 3 (3.7%) subjects in the sunitinib and placebo arms, respectively. There were no grade 5 AEs of hypoglycemia. Treatment-related hypoglycemia was reported as an AE for 4 (4.8%) and 1 (1.2%) subjects in the sunitinib and placebo arms, respectively. Four subjects (4.8%) in the sunitinib arm and 1 subject (1.2%) in the placebo arm reported treatment-emergent, all-causality AEs that were grade 3 or 4 in severity. Two subjects in the sunitinib arm had grade 3 or 4 events that were considered related to treatment. Subjects with grade 3/4 hypoglycemia are shown in Table 37.

**Table 37. Subjects with Grade 3 or 4 Hypoglycemia – Phase III Study A6181111**

Subject Number	Start/Stop Day	Grade	Outcome	Causality	Lowest Serum Glucose Level (mg/dL)
<b>Sunitinib (N=83)</b>					
10031008	124/126	3	Resolved	Study drug	56 (Day 127)
10491001	7/31	4	Resolved	Study drug	57.664 (Day 13)
10531002	2/3	4	Resolved	Disease under study	97.308 (Day 85)
10661008	12/13	3	Resolved	Diabetes	61.268 (Day 112)
<b>Placebo (N=82)</b>					
10421011	45/>60	4	Still present	Disease under study	131.55 (Day 28)

Abbreviations: N = number of subjects; Use of '>' represents imputed data.

Source: CSR Study A6181111

Of the 5 subjects with grade 3/4 hypoglycemia, only the subject on the placebo arm (Subject 10421011) had hypoglycemia recorded as medical history, although 1 subject on the sunitinib arm (Subject 10531002) had received glucagon pre-treatment (day -32) for hypoglycemia. Two of the 5 subjects (Subjects 10491001 and 10661008) had diabetes mellitus recorded as medical history. Subject 10491001 had undergone a pancreatic lesion excision (outcome: resected), Subject 10661008 had undergone a pancreaticosplenectomy (outcome: partially resected), and Subject 10421011 had undergone a pancreatectomy (outcome: resected) as prior surgeries.

Of these AEs, only the hypoglycemia experienced by Subject 10421011 was considered to be an SAE. One additional subject on the placebo arm (Subject 10091004) experienced an episode of grade 2 hypoglycemia that was considered to be an SAE.

#### 4.3.5.7. Clinical Laboratory Evaluations

Of the clinical laboratory data summarized in the following sections, abnormal values that the investigator determined to be clinically significant were reported as AEs.

##### 4.3.5.7.1. Hematology Abnormalities

CTCAE grade 3 or 4 hematology abnormalities were more common for the sunitinib arm than in the placebo arm (Table 38). These abnormalities represented shifts from CTCAE

grade ≤2 to grade ≥3 with the exception of grade 3 lymphocyte abnormality in 1 subject in the sunitinib arm, which was also grade 3 at baseline.

**Table 38. Summary of Number of Subjects with Grade 3 or 4 Hematology Abnormalities (All Cycles) – Phase III Study A6181111**

	Number (%) of Subjects			
	Sunitinib (N=82)		Placebo (N=80)	
	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) <sup>a</sup>	0	3 (3.8)	0

Abbreviation: N = number of subjects

<sup>a</sup>Abnormality was also Grade 3 at baseline for 1 of these subjects.

Source: CSR Study A6181111

#### 4.3.5.7.2. Chemistry Abnormalities

Chemistry data are summarized by maximum CTCAE severity in Table 39 (all cycles). As was the case with hematology abnormalities, grade 3 and 4 chemistry abnormalities were infrequently reported. Table 39 presents the most common abnormalities reported. Unlike the hematology abnormalities, the incidence of grade 3/4 chemistry abnormalities was similar in the sunitinib and placebo arms.

**Table 39. Summary of Selected CTCAE Grade 3 and 4 Chemistry Abnormalities and Shifts from Grade ≤2 to Grade ≥3 (All Cycles) – As-Treated Population – Phase III Study A6181111**

Parameter	Number (%) of Subjects with Highest CTCAE Grade of Abnormality		Number (%) of Subjects with Shift from CTCAE Grade ≤2	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Sunitinib (N = 82)</b>				
Alkaline phosphatase	8 (9.8)	0	4 (4.9)	0
Creatinine	1 (1.2)	3 (3.7)	1 (1.2) <sup>a</sup>	2 (2.4) <sup>a,b</sup>
Hyperglycemia	8 (9.8)	2 (2.4)	6 (7.3) <sup>b</sup>	1 (1.2) <sup>a</sup>
Hypophosphatemia	6 (7.4)	0	3 (3.8) <sup>a,c</sup>	0
<b>Placebo (N = 80)</b>				
Alkaline phosphatase	8 (10.0)	1 (1.3)	2 (2.5) <sup>b</sup>	1 (1.3) <sup>b</sup>
Creatinine	2 (2.5)	2 (2.5)	1 (1.3) <sup>a</sup>	1 (1.3) <sup>a</sup>
Hyperglycemia	13 (16.3)	1 (1.3)	9 (11.3) <sup>a,b,c</sup>	0
Hypophosphatemia	4 (5.2)	0	2 (2.6) <sup>a</sup>	0

Note: Table presents CTCAE Grade 3 and 4 chemistry abnormalities reported.

Abbreviations: N = number of subjects; CTCAE = Common Terminology Criteria for Adverse Events

<sup>a</sup> Includes at least 1 subject with a shift from CTCAE Grade 0;

<sup>b</sup> Includes at least 1 subject with a shift from CTCAE Grade 1;

<sup>c</sup> At least 1 additional subject had a missing/not reported CTCAE grade at baseline and a maximum CTCAE Grade 3.

Source: CSR Study A6181111

#### 4.3.5.7.3. Thyroid Function Tests

Prior and post-baseline TSH levels were recorded for 64/83 (77.1%) subjects on the sunitinib arm and 56/82 (68.3%) subjects on the placebo arm. Post-baseline TSH levels above the upper limit of normal (ULN) were recorded for 26/83 (31.3%) subjects on the sunitinib arm and 12/82 (14.6%) subjects on the placebo arm; post-baseline TSH levels below the LLN were recorded for 3/83 (3.6%) subjects on the sunitinib arm and 7/82 (8.5%) subjects on the placebo arm.

Two subjects, both on the placebo arm, had screening TSH levels ≥10 mIU/L.

Subject 1061002 had a TSH level of 25.1 mIU/L at screening; this increased to 200 mIU/L on day 58 but had declined to 7.8 mIU/L by day 282 and was ≤10.4 mIU/L at all subsequent measurements. Subject 10671004 had TSH levels of 12.25 mIU/L at screening, 8.97 mIU/L on day 12, and 5.19 mIU/L on day 25.

One subject with TSH <5 mIU/L at screening had a post-baseline TSH ≥20 mIU/L:

Subject 10411003 (sunitinib) had a screening TSH level of 1.5 mIU/L; TSH was ≤10.87 mIU/L at all post-baseline time points except on day 395. Free thyroxine (T<sub>4</sub>) was below the LLN on day 395 and within normal ranges at all other time points.

### **4.3.5.8. Vital Signs, Physical Examination Findings, and Electrocardiograms Related to Safety**

#### **4.3.5.8.1. Vital Signs**

When vital signs were measured during cycles 2-5, the mean changes from baseline in systolic and diastolic blood pressure were more marked for the sunitinib arm compared to the placebo arm; in 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 in the placebo arm. Mean heart rate and weight were similar in both treatment arms during all cycles.

Increases in blood pressure from baseline and absolute blood pressure values above defined thresholds were more common in the sunitinib arm than in 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 in each treatment arm had maximum systolic blood pressure >200 mmHg, and 8 and 1 subjects in the sunitinib and placebo arms, respectively, had maximum diastolic blood pressure >110 mmHg. Five of the 8 subjects on the sunitinib arm were being treated for hypertension at the start of the study. This group included 1 subject (Subject 10411003) who had treatment temporarily interrupted due to grade 3 hypertension, which was considered serious but had subsequently recovered. One subject on the sunitinib arm and none on the placebo arm discontinued the study because of an AE of hypertension.

#### **4.3.5.8.2. Physical Examination Findings**

Abnormal baseline findings were most commonly found in the abdomen (50/171 subjects, 29.2%). Clinically significant physical examination changes from baseline were recorded for 25/83 subjects (30.5%) in the sunitinib arm and 30/82 subjects (37.5%) in the placebo arm at the final visit.

#### **4.3.5.8.3. Electrocardiograms**

In both treatment arms, mean QTc and QTcF intervals were similar when measured in cycle 2 compared to the baseline measurement. Most subjects had QTc and QTcF intervals <450 msec.

One subject (in the sunitinib arm) had a QTc intervals  $\geq$ 500 msec. In an unscheduled ECG on day 68 (cycle 3), Subject 10661002 had a QTc interval of 519 msec, and this QTc interval prolongation was recorded as a CTCAE grade 3/4 abnormality. The subject was hospitalized on that day and experienced a number of SAEs, including ventricular arrhythmia and cardiac failure, and the subject died (See Section 4.3.5.3. Deaths; Table 33).

#### 4.3.6. Summary of Pivotal Phase III Study

The efficacy results of the pivotal Phase III Study A6181111 demonstrated a clinically significant improvement in the primary endpoint of PFS in subjects treated with sunitinib vs. placebo for advanced pancreatic NET. The magnitude of the effect was larger than postulated in the study design, leading to early termination of the study due to efficacy in combination with observed deaths and higher number of serious adverse events in the placebo arm. Of note, 95% of these subjects had metastatic disease with documented disease progression in <12 months of study enrollment. Also, the enrolled patients were not candidates for definitive surgery or other definitive therapy. The 6-7 month improvement in median PFS in the sunitinib arm as compared to the placebo arm was clinically significant by investigator assessment (11.4 vs. 5.5 months, HR = 0.418; 95% CI: 0.263 – 0.662;  $P = 0.000118$ ), algorithmic tumor assessment (12.6 vs. 5.4 months, HR = 0.401; 95% CI: 0.252 – 0.640;  $P = 0.000066$ ), and BICR assessment (12.6 vs. 5.8 months; HR = 0.315; 95% CI: 0.181 – 0.546;  $P = 0.000015$ ). The improvement in PFS was consistent across demography (such as age, race, gender), baseline and disease characteristics (such as ECOG PS, number of disease sites, presence or absence of extrahepatic distant metastases, histology, time from diagnosis), prior treatment (such as use of somatostatin analogs, number of prior systemic regimens) as well as Ki-67 indices. Cox proportional hazards modeling did not identify any confounding factors that would change the interpretation of the PFS advantage. However, univariate and multivariate Cox proportional hazards modeling for PFS did reveal a baseline characteristic that was prognostic, namely, time from diagnosis to randomization. Because of a slight imbalance of this factor in favor of the placebo arm, adjustment for this imbalance suggested an even greater treatment effect for sunitinib (HR = 0.374; 95% CI: 0.234, 0.599;  $P < 0.0001$ ). The biological basis for the prognostic value of this variable is unclear, although a shorter time from diagnosis to medical need for systemic therapy may reflect more aggressive disease.

Secondary endpoints further supported the benefit of sunitinib treatment in pancreatic NET. Sunitinib treatment was associated with a prolonged OS compared with placebo treatment (HR = 0.409; 95% CI: 0.187 - 0.894;  $P = 0.0204$ ; 30 OS events). Patients treated with sunitinib had a statistically significant increase in ORR compared to the patients treated with placebo in both the investigator overall assessment and the algorithmic tumor assessment (9.3% vs. 0%, respectively; 95% CI: 3.2 - 15.4;  $P = 0.0066$ ). Of note, the ORR on the sunitinib arm may have been an underestimation due to the early termination of this study.

Fewer subjects treated with sunitinib initiated the use of disease-specific concomitant medications during study, including a somatostatin analog, than subjects treated with placebo. Global health-related quality of life and functioning domains were maintained for subjects on sunitinib treatment with limited adverse symptomatic effects.

The AE profile of sunitinib was generally tolerable. Common sunitinib-related AEs were consistent with those that have previously been reported, such as diarrhea, nausea, asthenia, vomiting, and fatigue. Most of these AEs were grade 1 or 2 in severity, although grade 3/4 AEs did appear to be more common on the sunitinib arm. SAEs were more common on the placebo arm (41.5%) as compared to the sunitinib arm (26.5%), although treatment-related SAEs were more common on the sunitinib arm (13.3% compared to 7.3% of placebo

subjects). Subjects on the sunitinib arm were on study longer than in the placebo group (median duration of days on study was 141 and 113 days, respectively); therefore, there was a greater opportunity to experience AEs on the sunitinib arm. Grade 3/4 hematologic abnormalities were also more common on the sunitinib arm compared to the placebo arm.

The AE profile of sunitinib was generally manageable by dosing interruption, dose reduction, and/or conventional standard medical therapy. The incidence of permanent discontinuation due to AEs was modestly higher on the sunitinib arm (18/83 subjects, 21.7%) as compared to the placebo arm (14/82 subjects, 17.1%). 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%). Majority of deaths were due to the disease under study. One subject on the sunitinib arm died due to an AE of cardiac failure, and 1 subject on the placebo arm died due to an AE of dehydration, and both cases were considered to be treatment-related by the investigator.

## 5. CLINICAL PHARMACOLOGY

### 5.1. Overview

This section provides supportive pharmacokinetic information in subjects with pancreatic NET in comparison to subjects with GIST and RCC, and for the CDD schedule in comparison to Schedule 4/2 in GIST and RCC subjects.

In the pancreatic NET sNDA, new supportive pharmacokinetic data (i.e., steady state trough) were provided from 1) Study RTKC-511-015, a Phase II safety/tolerability pharmacokinetic study in carcinoid tumor and pancreatic NET on Schedule 4/2 with starting sunitinib dose of 50 mg; 2) Study A6181047, a Phase II open label safety/tolerability pharmacokinetic study in GIST on CDD schedule with starting sunitinib dose of 37.5 mg; and 3) Study A6181061, a Phase II open label safety/tolerability pharmacokinetic study in RCC on CDD schedule with starting sunitinib dose of 37.5 mg. The data from the above 3 studies in combination with the previously submitted pharmacokinetic data, part of the original NDA for GIST (Studies RTKC-0511-013 and A6181004) and RCC (Studies RTKC-0511-014 and A6181006) on Schedule 4/2 with starting dose of 50 mg, were used to compare the pharmacokinetics of sunitinib and its active metabolite in pancreatic NET to GIST and RCC as well as comparing the CDD schedule to Schedule 4/2 in GIST and RCC.

### 5.2. Comparison and Analyses of Results Across Studies

#### 5.2.1. Carcinoid Tumor and Pancreatic NET versus Other Tumor Types

The steady state trough concentrations for sunitinib, SU012662, and total drug in subjects with carcinoid tumor and pancreatic NET have been evaluated in Study RTKC-0511-015. The steady state trough concentrations from studies RTKC-0511-015 in NET subjects, RTKC-0511-013 and A6181004 in GIST subjects, and RTKC-0511-014 and A6181006 in RCC subjects are presented in Table 40.

The mean  $C_{\text{trough}}$  values for sunitinib were 52.8 ng/mL, 57.7 ng/mL, 44.9-49.2 ng/mL, and 51.9-64.0 ng/mL in pancreatic NET, carcinoid tumor, GIST, and RCC subjects, respectively. In addition, for SU012662, mean  $C_{\text{trough}}$  values were 24.6 ng/mL, 25.0 ng/mL, 22.4-22.8

ng/mL, and 30.8-30.9 ng/mL in pancreatic NET, carcinoid tumor, GIST, and RCC subjects, respectively. Similarly, for total drug, mean C<sub>trough</sub> values were 77.4 ng/mL, 82.7 ng/mL, 67.7-71.7 ng/mL, and 82.7-94.9 ng/mL in pancreatic NET, carcinoid tumor, GIST, and RCC subjects, respectively. Overall, the steady state trough plasma exposures to sunitinib, SU012662, and total drug appeared to be similar in pancreatic NET subjects as compared to GIST and RCC subjects, supporting lack of tumor type dependence in the PK of sunitinib and SU012662. In addition, the intersubject variabilities for sunitinib, SU012662, and total drug C<sub>trough</sub> were similar in subjects with pancreatic NET to those in GIST and RCC. Similarly, the steady state trough plasma exposures to sunitinib, SU012662, and total drug and their respective intersubject variabilities in the pancreatic NET subpopulation appeared to be similar to those in the carcinoid tumor subpopulation, suggesting that the PK of sunitinib and SU012662 in subjects with each of these two important NET subpopulations is similar.

**Table 40. Summary of Sunitinib, SU012662 and Total Drug Steady State Dose-Corrected Trough Concentrations Following Multiple 50-mg Doses of Sunitinib (Studies RTKC-0511-015, A6181004, A6181006, RTKC-0511-013, and RTKC-0511-014) in Cycle 1**

Parameter	Arithmetic Mean (CV%) [Median]					
	NET(P)		NET(C)		RCC	
	Study	Study	Study	Study	Study	Study
	015	015	1004	013	014	1006
	Schedule	Schedule	Schedule	Schedule	Schedule	Schedule
	4/2	4/2	4/2	4/2	4/2	4/2
	Day 14	Day 14	Day 28	Day 29	Day 28	Day 28
	(n=57)	(n=36)	(n=84)	(n=5)	(n=20)	(n=38)
<b>Sunitinib</b>						
DC-C <sub>trough</sub> (ng/mL)	52.8 (51) [52.2]	57.7 (49) [55.7]	49.2 (44) [45.8]	44.9 (40) [35.4]	64.0 (36) [63.7]	51.9 (42) [48.3]
<b>SU012662</b>						
DC-C <sub>trough</sub> (ng/mL)	24.6 (56) [22.6]	25.0 (51) [25.3]	22.4 (64) [19.2]	22.8 (69) [14.6]	30.9 (41) [28.5]	30.8 (54) [29.1]
<b>Total Drug</b>						
DC-C <sub>trough</sub> (ng/mL)	77.4 (50) [75.2]	82.7 (44) [78.6]	71.7 (46) [67.3]	67.7 (49) [48.4]	94.9 (34) [93.2]	82.7 (43) [76.0]

Abbreviations: n = number of subjects with observations; CV = coefficient of variation; DC-C<sub>trough</sub> = dose-corrected trough concentration; GIST = gastrointestinal stromal tumors; RCC = renal cell carcinoma; NET(C) = carcinoid neuroendocrine tumor; NET(P) = pancreatic neuroendocrine tumor.

Source: Summary of Clinical Pharmacology; CSR Study A6181004; CSR Study RTKC-0511-013; CSR Study RTKC-0511-014; CSR Study A6181006

### 5.2.2. Continuous Daily Dosing versus Intermittent Dosing

The dose proportionality of plasma exposures to sunitinib, SU012662, and total drug has been previously evaluated in advanced cancer subjects following single sunitinib doses ranging from 50 to 350 mg, and multiple daily dosing with doses of 25 to 100 mg (on Schedule 4/2). The dose-corrected maximum and total plasma exposures were comparable between doses and showed no dose-related trends, demonstrating that the PK of sunitinib,

SU012662, and total drug were dose-proportional or close to dose-proportional over the dose ranges evaluated following both single and multiple dosing. Similarly, the dose-corrected AUC<sub>24</sub> values (at steady state) after multiple day dosing were similar to AUC<sub>∞</sub> values after single dosing, supporting lack of time-dependence in the PK of sunitinib, SU012662, and total drug. Consistent with the linearity in PK, it has been observed that the PK disposition of sunitinib, SU012662, and total drug was similar among dosing Schedules 4/2, 2/1, and 2/2. To further support the linearity in the PK of sunitinib, SU012662, and total drug on schedule CDD, the steady state trough values for sunitinib, SU012662, and total drug on schedule CDD were compared to Schedule 4/2.

The steady state trough concentrations of sunitinib, SU012662, and total drug on schedules CDD and 4/2 are presented in Table 41. The dose-corrected mean C<sub>trough</sub> values for sunitinib ranged from 40.9-64.2 ng/mL on Schedule CDD and 42.6-57.9 ng/mL on Schedule 4/2. In addition, for SU012662, mean dose-corrected C<sub>trough</sub> values ranged from 15.9-25.3 ng/mL on Schedule CDD and 21.0-32.7 ng/mL on Schedule 4/2. Similarly, for total drug, mean dose-corrected C<sub>trough</sub> values ranged from 58.2-87.5 ng/mL on Schedule CDD and 63.6-87.2 ng/mL on Schedule 4/2. There was a significant overlap between the dose-corrected trough plasma concentrations for sunitinib, SU012662, and total drug between Schedule CDD and Schedule 4/2, supporting lack of schedule dependence in the PK of sunitinib and SU012662. Therefore, it would be expected that the total plasma exposure to sunitinib and SU012662 following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2 (ie, 37.5 mg × 42 days ≈ 50 mg × 28 days).

**Table 41. Summary of Sunitinib, SU012662 and Total Drug Steady State Dose-Corrected Trough Concentrations Following Multiple 37.5-mg or 50-mg Doses of Sunitinib (Studies A6181004, A6181006, A6181047, and A6181061)**

Parameter	Arithmetic Mean (CV%) [Median]			
	Schedule CDD		Schedule 4/2	
	Study 1047	Study 1061	Study 1004	Study 1006
	GIST	RCC	GIST	RCC
	Cycles 2-13	Cycles 2-12	Cycle 1-8	Cycles 1-4
	Day 1	Day 1	Day 28	Day 28
	(n=4-25)	(n=6-22)	(n=5-84)	(n=9-38)
<b><u>Sunitinib</u></b>				
DC-C <sub>trough</sub> (ng/mL)	41.9-58.6 (30-61) [33.5-53.3] <sup>a</sup>	40.9-64.2 (25-89) [40.0-59.1] <sup>a</sup>	42.6-57.9 (16-55) [44.9-61.8]	48.7-56.2 (42-50) [48.3-56.2]
<b><u>SU012662</u></b>				
DC-C <sub>trough</sub> (ng/mL)	17.4-25.3 (34-56) [16.1-24.9] <sup>a</sup>	15.9-24.9 (32-65) [14.5-23.3] <sup>a</sup>	21.0-31.1 (31-74) [18.1-26.9]	29.4-32.7 (47-70) [22.2-34.8]
<b><u>Total Drug</u></b>				
DC-C <sub>trough</sub> (ng/mL)	60.0-83.7 (26-57) [56.7-79.7] <sup>a</sup>	58.2-87.5 (24-78) [54.9-78.9] <sup>a</sup>	63.6-86.7 (18-54) [67.3-87.4]	80.9-87.2 (43-50) [76.0-91.9]

Abbreviations: CDD = continuous daily dosing; CV = coefficient of variation; DC-C<sub>trough</sub> = dose-corrected trough concentration; GIST = gastrointestinal stromal tumor; n = number of subjects with observations; RCC = renal cell carcinoma; <sup>a</sup> Dose corrected to 50 mg.

Source: CSR Study A6181047; CSR Study A6181061; CSR Study A6181004; CSR Study A6181006

Based on the PK data in pancreatic NET (Table 40), the predicted steady state trough mean plasma concentrations in pancreatic NET following administration of sunitinib 37.5 mg on Schedule CDD would be 39.6 ng/mL for sunitinib, 18.5 ng/mL for SU012662, and 58.1 ng/mL for total drug. These predicted trough concentrations in pancreatic NET would be similar to the trough concentrations for sunitinib, SU012662, and total drug following administration of sunitinib 37.5 mg on Schedule CDD in GIST (eg, 38.4 ng/mL, 13.6 ng/mL, and 52.0 ng/mL on day 1 of cycle 2, respectively); and RCC (eg, 41.6 ng/mL, 15.4 ng/mL, and 56.9 ng/mL on day 1 of cycle 2, respectively).

### 5.3. Dosing Recommendations Based on Clinical Pharmacology Data

The recommended dose of sunitinib for the treatment of subjects with pancreatic NET is 37.5 mg orally, taken once daily on Schedule CDD.

The steady state trough plasma exposures to sunitinib and its active metabolite SU012662 in the pancreatic NET subpopulation appeared to be similar to that in GIST and RCC, indicating that the PK of sunitinib and SU012662 were not tumor type-dependent with respect to GIST, RCC, and pancreatic NET.

In addition, the PK of sunitinib and SU012662 appeared to be similar between schedules CDD and 4/2 in GIST and RCC subjects. Therefore, it would be expected that the total plasma exposure to sunitinib and SU012662 following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2, also supporting the selection of a 37.5-mg dose on a CDD schedule for supplemental registration in pancreatic NET.

## 6. SUMMARY AND CONCLUSIONS

Sunitinib, an oral multi-targeted receptor tyrosine kinase inhibitor with demonstrated efficacy in GIST and RCC, is proposed for the treatment of patients with unresectable pancreatic NET. Supporting the proposed indication are the data from the pivotal, randomized, double-blind, placebo-controlled Phase III trial of sunitinib 37.5 mg on a CDD schedule in patients with progressive, well-differentiated pancreatic NET. Treatment with sunitinib yielded more than double the PFS compared to treatment with placebo (11.4 vs. 5.5 months; HR = 0.418; 95% CI 0.263, 0.662;  $P = 0.000118$ ) translating into more than 50% reduction in the relative risk of disease progression or death from any cause in subjects with pancreatic NET. This improvement in PFS was independent of baseline characteristics. Improvements in secondary efficacy endpoints of ORR (9.3% vs. 0%;  $P = 0.0066$ ) and OS (HR = 0.409; 95% CI 0.187, 0.894;  $P = 0.0204$ ) in the sunitinib arm further supported the primary outcome. Due to the favorable benefit/risk for sunitinib compared with placebo in patients with progressive, well-differentiated pancreatic NET, the independent DMC recommended stopping the Phase III study and the sponsor accepted this recommendation. Upon discontinuation of the study, patients in the placebo arm were allowed to receive treatment with sunitinib. This recommendation was based on the prolonged PFS reported in the sunitinib arm and the observation of a higher number of deaths and serious adverse events in the placebo arm. Two subsequent efficacy analyses, based on algorithmic assessment data

and a blinded independent central review, are consistent with the primary finding confirming the robustness of the data and the benefit of sunitinib in pancreatic NET.

Additionally, fewer subjects treated with sunitinib than placebo initiated the use of disease-specific concomitant medications, such as somatostatin analogues, on study. The safety results demonstrate the AE profile of sunitinib was generally tolerable and clinically manageable. Common sunitinib-related AEs were consistent with those that have previously been reported with sunitinib, such as diarrhea, nausea, asthenia, vomiting, and fatigue, and were primarily mild to moderate in severity. Although AEs, SAEs, and deaths were experienced by more subjects in the placebo arm, treatment-related AEs and SAEs were reported to be higher in the sunitinib arm. There were 2 treatment-related deaths, one in each arm. Global health-related quality of life and functioning domains were maintained for subjects on sunitinib treatment with limited adverse symptomatic effects. Therefore, the efficacy advantage for sunitinib was observed in pivotal Study A6181111 across all efficacy endpoints with an acceptable safety profile.

The efficacy and safety results of the Phase II study of sunitinib 50 mg on Schedule 4/2 in the pancreatic NET cohort supported the outcomes of the pivotal Phase III study. Sunitinib treatment, at a starting dose of 50 mg daily for 4 consecutive weeks in repeated 6-week cycles, produced a clinically significant ORR of 16.7% (all PRs, 95% CI: 8.6 – 27.9) in the pancreatic NET cohort. The partial responses were durable (DR range: 1.4+ to 12.5+ months). Median TTP based on Kaplan-Meier analysis was 7.8 months (95% CI: 6.6 – 12.6). The toxicity profile of sunitinib was generally tolerable and manageable at Schedule 4/2. The AE profile of sunitinib was similar to that observed in other clinical studies and attributed to pancreatic NET. The AEs included gastrointestinal, constitutional, cutaneous, and myelosuppressive events, generally mild to moderate severity. One death was attributed to sunitinib treatment.

The PK of sunitinib and its active metabolite SU012662 were not tumor type-dependent with respect to GIST, RCC, and pancreatic NET. As the PK of sunitinib and SU012662 were similar between Schedules CDD and 4/2 in GIST and RCC subjects, it is expected that the total plasma exposure to sunitinib and SU012662 following treatment with sunitinib 37.5 mg on a CDD schedule would be similar to that following treatment with sunitinib 50 mg on Schedule 4/2 in pancreatic NET. These data support the selection of sunitinib at 37.5-mg dose on a CDD schedule for supplemental registration in pancreatic NET.

The results from Phase II and Phase III studies demonstrate significant clinical benefit with sunitinib treatment in patients with progressive, well-differentiated, advanced, unresectable pancreatic NET. Treatment with sunitinib has successfully addressed a high unmet medical need by demonstrating a favorable benefit/risk profile for the treatment of patients with pancreatic NET. Clinically and statistically significant increases in OS and ORR, respectively, also supported these primary outcomes, as did the maintenance of improvement in health-related quality of life. Therefore, the demonstration of clinical benefit of sunitinib in subjects with pancreatic NET builds upon the proven clinical safety and efficacy in patients with solid tumors driven by VEGFR/PDGFR and KIT signaling.

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