FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

April 12, 2011

NDA 21938/S013
Sutent® (sunitinib malate)
Applicant: Pfizer, Inc.

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TABLE OF CONTENTS

1 PROPOSED INDICATION 3

2 EXECUTIVE SUMMARY 3

3 DRUG DESCRIPTION 4

4 BACKGROUND ON PANCREATIC NET (PNET) 4

5 REGULATORY HISTORY OF SUNITINIB DEVELOPMENT PROGRAM IN PNET 5

6 A6181111 STUDY 6

6.1 Study Design 6
6.1.1 Eligibility 6
6.1.2 Treatment 6
6.1.3 Safety Assessments 6
6.1.4 Efficacy Assessments 6
6.1.5 Statistical Analysis Plan 7
6.1.5.1 Definition of PFS and Censoring Rules 7
6.1.5.2 Power calculation, sample size estimation, interim and final PFS analysis 7
6.1.6 Protocol Amendments 7
6.2 Study Results 8
6.2.1 Patient Disposition 8
6.2.2 Patient Demographics and Disease Characteristics 8
6.2.3 Protocol Deviations 10
6.3 Efficacy Results 10
6.3.1 Early Study Termination 10
6.3.2 Analysis of Primary Endpoint 10
6.3.2.1 Sponsor Analysis of Investigator Determined PFS 10
6.3.2.2 *Post-hoc* Blinded Independent Central Radiologic Review (BICR) 12
6.3.2.3 FDA analysis of PFS 13
6.3.2.4 Summary of PFS analyses 14
6.3.2.5 Potential Overestimation of Magnitude of PFS Treatment Effect 15
6.3.3 Analysis of Secondary Endpoints 16
6.3.3.1 Overall Survival 16
6.3.3.2 Objective Response Rate 17
6.3.3.3 Patient-reported outcomes (PRO) 17
6.4 Safety Results 17
6.4.1 Exposure Summary 18
6.4.2 Deaths 18
6.4.3 Nonfatal Serious Adverse Events (SAE) and Grade 3-4 Adverse Events 18
6.4.4 Common Adverse Events 19
6.4.5 Discontinuations due to Adverse Event 20

7 CONCLUSIONS 21

1 Proposed Indication

"Sunitinib is a kinase inhibitor indicated for the treatment of unresectable pancreatic neuroendocrine tumors (PNET)."

2 Executive Summary

The pivotal study for this efficacy supplement is A6181111, sponsored by Pfizer.

Study A6181111 was a multicenter, multinational, double-blind, randomized Phase 3 trial comparing sunitinib to placebo in 171 subjects with locally advanced or metastatic well-differentiated pancreatic neuroendocrine tumors (PNET). Patients could have received any number of prior regimens or be treatment-naive, and must have had RECIST-defined progression within 2-12 months prior to screening. Patients were randomized 1:1 to sunitinib (37.5 mg orally continuous daily dosing) or placebo. The primary efficacy endpoint was investigator-determined progression-free survival (PFS). Secondary endpoints included overall survival (OS) and objective response rate (ORR).

FDA would like the ODAC members to consider the following issues:

The **first** issue is the early closure of the trial. The primary efficacy endpoint was investigator-determined PFS. The Data Monitoring Committee (DMC) took several unplanned looks at the efficacy data and recommended closure after 73 PFS events, representing 28% of the 260 planned PFS events. The study was terminated after 81 PFS events, or 31% of planned events. This is well before the pre-specified interim analysis of 130 PFS events. The early signal of improved PFS with sunitinib did not cross a pre-specified efficacy boundary. Stopping trials prematurely for efficacy may overestimate the magnitude of the observed treatment effect

The **second** issue is the uncertain clinical benefit of sunitinib in PNET, which can have a relatively indolent natural history. The ODAC will be asked to discuss the benefit:risk assessment of an estimated 5-6 month improvement in median PFS taking into consideration: (1) possible overestimation of PFS effect due to multiple looks at the data and early trial closure; (2) no statistically significant improvement in OS; (3) no demonstrated improvement in patient reported outcomes or symptom benefit (with a detriment in diarrhea symptom score); and (4) increased frequency of common adverse events (such as diarrhea, nausea, fatigue, hand-foot syndrome, stomatitis, and neutropenia), and rare but life-threatening adverse events (such as leukoencephalopathy, intracranial hemorrhage, renal failure, hepatic toxicity, ventricular arrhythmia, and cardiac failure). FDA is concerned that the magnitude of PFS effect from a prematurely terminated small single study is uncertain. When the efficacy magnitude is uncertain, the benefit:risk assessment may also be uncertain.

3 Drug Description

Sunitinib is a small molecule receptor tyrosine kinase (RTK) inhibitor that blocks signaling of multiple RTKs, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), KIT and FLT-3. Sunitinib is FDA approved for: (1) imatinib refractory or intolerant GIST, and (2) locally advanced or metastatic renal cell carcinoma. The approved dose for these indications is 50 mg orally daily for 4 weeks, followed by 2 weeks off. The proposed dosing regimen for the sunitinib PNET efficacy supplement is 37.5 mg orally, continuous daily dosing.

4 Background on Pancreatic NET (PNET)

Pancreatic NETs (PNETs), also known as well-differentiated pancreatic islet cell tumors, are rare. An analysis of the SEER database from 2000 to 2004 estimates an annual age-adjusted incidence of 0.32 per 100,000 adults in the United States (Yao JC *et al* JCO 2008). PNETs are distinct from the more common adenocarcinoma of the exocrine pancreas. While by incidence PNETs account for only 1.3% of all pancreatic cancers, because of superior prognosis, they represent almost 10% of pancreatic cancer in prevalence analyses.

The 2000 WHO criteria classify PNET into: (1) WHO I: well differentiated endocrine tumor confined to the pancreas of benign behavior (<2 cm in size, <2% Ki-67) or uncertain behavior (≥2cm in size, >2% Ki-67) (2) WHO II: well differentiated endocrine carcinoma with gross local invasion and/or metastasis. and (3) WHO III: poorly-differentiated endocrine carcinoma. The patient population studied in this application is locally advanced/metastatic well-differentiated PNET (WHO classification II).

Pancreatic NETs can be either functional (producing peptides which cause characteristic hormonal syndromes) or nonfunctional. Generally, five categories of functional PNETs are recognized – insulinoma (typically benign), gastrinoma, glucagonoma, VIPoma, and a group of 'other' types (i.e. polypeptidoma and somatostatinoma). PNETs can arise sporadically or as a result of familial cancer predisposition syndromes such as MEN1, TSC2, NF1 and VHL.

Although typically slow growing with low mitotic activity, most PNETs are malignant and metastasize commonly to lymph nodes and liver and less commonly to bone, lung, brain, and other organs. Locally invasive/metastatic PNETs can be aggressive, although precise outcome data are elusive due to the rarity of the tumor. In a retrospective analysis of the SEER database between 1988 to 2004, the median overall survival for patients diagnosed with well- to moderately-differentiated PNET was not reached for localized disease, 111 months for regional disease, and 27 months for metastatic disease. The 10 year survival rate was 58% for localized disease, 46% for regional disease, and 11% for distant disease (Yao JC *et al* JCO 2008).

There are two FDA approved systemic treatments for the treatment of PNET. Zanosar (streptozocin) was approved by the FDA in 1982 based on response rates observed in patients with functional and nonfunctional pancreatic islet cell tumors (Broder LE *et al*, Ann Intern Med 1973). Studies combining Zanosar with 5FU and/or doxorubicin have shown response rates ranging from 39 to 69% with combination chemotherapy (Moertel CG *et al* NEJM 1980; Kouvaraki MA *et al* JCO 2004). Sandostatin (octreotide acetate) was approved by the FDA in 1998 for symptomatic treatment of diarrhea and flushing episodes associated with carcinoid syndrome and VIPomas.

In addition to Zanosar and Sandostatin, there are other palliative treatments for advanced metastatic PNET, including liver directed therapies such as hepatic artery embolization and chemoembolization, hepatic metastectomy and transplantation, and radiofrequency ablation and cryoablation.

5 Regulatory history of sunitinib development program in PNET

There was no End of Phase 2 meeting or Special Protocol Assessment with the FDA for the sunitinib PNET development program. The Phase 3 PNET study was conducted from June 2007 to April 2009. The supplemental NDA was initially submitted in December 2009.

In May 2010, the FDA issued the sponsor a Complete Response letter for the sunitinib PNET efficacy supplement. The FDA was concerned that the study was prematurely terminated as a result of unplanned interim analyses after only 28% of the planned PFS events were observed. In addition, there was concern about un-blinding due to differences in frequency of adverse events between the sunitinib and placebo arms, which could have introduced bias in investigator determination of PFS. Finally, an FDA analysis of the data showed a reduced magnitude of effect on PFS when strictly applying RECIST criteria and appropriately censoring for missing and incomplete assessments.

Given these concerns, the FDA requested: (1) a *post-hoc* blinded independent central radiologic review of PFS events for all 171 subjects enrolled in the Phase 3 trial, and (2) a recalculation of investigator determined PFS applying strict RECIST criteria and appropriate censoring for missing data according to the 2007 FDA “Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.”

In December 2010, the sponsor resubmitted the PNET efficacy supplement.

6 A6181111 study

6.1 Study Design

6.1.1 Eligibility

Patients had locally advanced or metastatic well-differentiated pancreatic islet cell tumor that had progressed (by RECIST criteria) on a scan (CT, MRI, or Octreoscan) within 2 to 12 months prior to baseline compared to a previous scan. While the requirement was progression within 2-12 months prior to enrollment, data on when and how patients progressed was not collected in the case report forms.

Patients had disease not amenable to surgery, radiation, or combined modality therapy with curative intent and measurable by RECIST criteria. In addition, adequate organ function and an ECOG performance status (PS) of 0 or 1 was required. Patients could be treatment naive or could have received any number of previous treatments including chemotherapy, loco-regional therapy (e.g. chemoembolization) or interferon, provided that toxicities had recovered to grade 1 or less and it was at least four weeks prior to baseline assessment. Concomitant somatostatin analogue use was permitted while on study.

6.1.2 Treatment

Patients were randomized 1:1 to either sunitinib (37.5 mg oral continuous daily dosing) or matching placebo using a centralized registration system. Randomization was balanced by country/region. No other stratification factors were used.

Patients were treated until progression by RECIST criteria (as determined by the investigator) or unacceptable toxicity. At the time of progression, placebo-treated patients were un-blinded and offered cross-over to sunitinib in an open label continuation study.

6.1.3 Safety Assessments

EKG was assessed at baseline, week 5 and at the end of treatment. MUGA or echocardiogram was assessed at screening. Physical examination, vital signs, and urine protein dipstick were performed at screening, week 5, and every 4 weeks thereafter. Hematology, blood chemistry, and thyroid function testing were performed at screening, week 3, week 5, and every 4 weeks thereafter.

6.1.4 Efficacy Assessments

Tumor imaging was performed at screening, week 5, week 9, and every 8 weeks thereafter. Computed tomography or MRI scans at screening included chest, abdomen, pelvis and brain as well as a bone scan. Subsequent scans may have included only areas

of known or suspected tumors. Additional scans were performed whenever disease progression was suspected, to confirm a partial or complete response, and at the time of withdrawal from the study.

6.1.5 Statistical Analysis Plan

6.1.5.1 Definition of PFS and Censoring Rules

The primary endpoint, PFS, was defined as the time from randomization to progression of disease (PD) by RECIST (version 1.0) criteria, as determined by the investigator, or death for any reason in the absence of documented PD. Subjects who underwent radiation were considered to have PD. PFS data was 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, who started a new anti-cancer therapy prior to documented PD, or who had documented PD or died after two or more consecutive missing tumor assessments. Additionally, subjects lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with duration of 1 day.

6.1.5.2 Power calculation, sample size estimation, interim and final PFS analysis

For the final PFS analysis, a log-rank test (two-sided) was to be used to compare PFS between the two treatments with nominal significance level of 0.049 (2-sided), after an adjustment for one planned interim analysis at 130 PFS events. Study A6181111 was designed to have 90% power to detect a 50% improvement (hazard ratio of 0.67) in median PFS from 22 weeks (5.1 months) to 33 weeks (7.6 months) in patients randomized to receive sunitinib. The corresponding planned sample size was 340 patients to observe 260 PFS events.

One interim analysis was planned at 130 PFS events; and Lan-DeMets methodology was to be used for alpha spending. The estimated significance level for the interim efficacy PFS analysis was 0.0031.

Secondary endpoints included overall survival (OS), objective response, duration of response, and time to tumor response.

6.1.6 Protocol Amendments

Amendment 3, approximately 8 months after accrual began, installed an independent data monitoring committee (DMC). The DMC had access to un-blinded subject treatment assignment. In addition to monitoring the safety of subjects, the DMC was to be involved in the conduct and interpretation of the pre-specified interim analysis of efficacy at 130 PFS events. At the interim analysis, the DMC was to provide the sponsor with a recommendation to continue the trial as planned, to adjust the sample size, or to discontinue the trial. Of note, the protocol amendment did not state that the DMC would review efficacy data prior to the pre-specified interim analysis.

6.2 Study Results

6.2.1 Patient Disposition

A total of 42 centers in 11 countries across four regions (Western Europe, Asia, Australia, and North America) enrolled 171 subjects onto this study. The majority of subjects were recruited from Europe (67%), primarily France (35%), followed by North America (20%). There were 14 subjects (8%) enrolled in the United States.

The efficacy analysis was based on 171 randomized patients (86 sunitinib, 85 placebo) who comprise the intent to treat (ITT) population. Six subjects, three on each arm, were randomized but not treated (5 due to study termination and 1 due to eligibility violation). The safety analysis is comprised of the 'As treated' population (165 total, 83 sunitinib, 82 placebo).

6.2.2 Patient Demographics and Disease Characteristics

Table 1 summarizes baseline patient demographics and disease characteristics. There were certain imbalances (such as performance status, number of disease sites, number with distant extra-hepatic metastasis, and number with prior liver directed therapies) that potentially favored the sunitinib arm.

Table 1: Patient demographic and baseline characteristics

	Sunitinib (n=86)	**Placebo (n=85)**
Gender n(%)		
Male	42 (49%)	40 (47%)
Female	44 (51%)	45 (53%)
Age [Median (Range)]	56 (25 – 84)	57 (26 – 78)
Race n(%)		
White	48 (56%)	53 (62%)
Asian	13 (15%)	10 (12%)
Other	25 (29%)	21 (25%)
Unspecified	0 (0%)	1 (%)
ECOG PS		
0	53 (62%)	41 (48%)
1	33 (38%)	43 (51%)
2	0	1 (1%)
Baseline Tumor Characteristics		
Non-functioning	42 (49%)	44 (52%)
Functioning	25 (29%)	21 (25%)
Gastrinoma	9 (11%)	10 (12%)
Glucagonoma	3 (3%)	2 (2%)
Insulinoma	2 (2%)	2 (2%)
VIPoma	0 (0%)	2 (2%)
Other	11 (13%)	5 (6%)
Unknown	19 (22%)	20 (24%)
Ki-67 Index		
Subjects with Ki-67 Index Reported	36 (42%)	36 (42%)
≤2%	7 (8%)	6 (7%)
>2%-5%	16 (19%)	14 (16%)
≥5%	13 (15%)	16 (19%)
Subjects with Ki-67 not reported	50 (58%)	49 (58%)
Median Time from Diagnosis, years	2.4 (0.1-25.6)	3.2 (0.1-21.3)
Median Sum of Target Lesions, cm	15.7 (1.1-54.4)	15.9 (1.0-46.2)
Number of Involved Sites		
1-2 sites	61 (71%)	49 (58%)
≥3 sites	24 (28%)	35 (41%)
Not Reported	1 (1%)	1 (1%)
Distant metastasis (including liver)	82 (95%)	80 (94%)
Distant extra-hepatic metastasis	21 (24%)	34 (40%)
Prior Cancer Therapies		
Prior pancreatic tumor resection	47 (55%)	49 (58%)
Prior hepatic tumor resection	18 (21%)	21 (25%)
Prior Radiation	9 (11%)	12 (14%)
Prior Liver Directed therapies	11 (13%)	22 (26%)
Prior Chemotherapy	45 (52%)	50 (59%)
1-2 Systemic Regimens	35 (41%)	38 (45%)
≥3 Systemic Regimens	10 (12%)	12 (14%)
Baseline Somatostatin Analogue	21 (24%)	16 (19%)

6.2.3 Protocol Deviations

At least 8 subjects (4.6%) did not progress within 2 to 12 months prior to screening, although this may be an underestimate as the date of prior progression was not documented in the case report forms. Other notable deviations included: 1 subject with the wrong diagnosis (rectal neuroendocrine tumor), 3 subjects with a lack of measureable disease, and 1 subject with an ECOG PS of 2.

6.3 Efficacy Results

6.3.1 Early Study Termination

The DMC met three times to review safety data, (May 2008; November 2008; and February 2009), at which times, PFS data was also reviewed (based on 20, 50, and 73 PFS events, respectively). These DMC efficacy reviews were not pre-specified and no alpha was allocated for them in the Statistical Analysis Plan (SAP). At the November 2008 meeting, when 50 PFS events had been observed, the DMC stated that "given the marked PFS difference between arms it would be reasonable to consider closure at an earlier time," and decided to meet again in 3 months, instead of 6 months.

In February 2009, at its third meeting, the DMC recommended closure of Study A6181111 based on its review of preliminary safety and efficacy data after only 73 PFS events (28.1% of planned events) had been observed. This recommendation was based on an observed median PFS of 11.1 months on sunitinib versus 5.5 months on placebo with corresponding hazard ratio (HR) of 0.397, 95% confidence interval (CI) (0.243, 0.649), and 2-sided unstratified log-rank test p-value 0.0002. However, no formal alpha spending and statistical stopping boundaries were implemented. The DMC noted that if the study continued as planned and the interim analysis at 130 events was conducted, there would have been a 91% chance (conditional power) of stopping the study assuming that the true HR was 0.649 (upper limit of the 95% CI of the observed HR at 73 events). Thus, the DMC claimed that the study had met its primary endpoint in demonstrating a significant PFS advantage for sunitinib.

The sponsor agreed with the DMC and notified all investigators in March 2009 that the study would be closed and all patients (regardless of whether they had PD or not) should be offered open-label sunitinib on one of two extension studies (A6181078 or A6181114). The final PFS analysis was based on all PFS events reported by April 15, 2009 (the data cutoff date), at which time, there were 171 patients enrolled and 81 PFS events (31.2% of planned events) observed.

6.3.2 Analysis of Primary Endpoint

6.3.2.1 Sponsor Analysis of Investigator Determined PFS

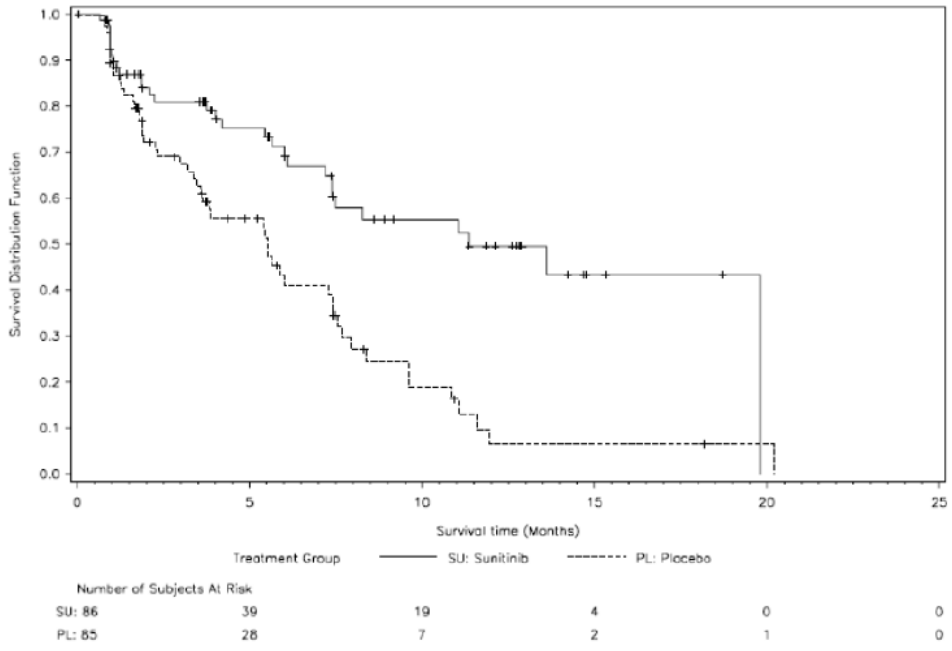
The primary analysis of investigator-determined PFS is shown in Table 2 and Figure 1:

Table 2: Investigator PFS analysis (ITT population)

	Sunitinib (n=86)	**Placebo (n=85)**
Number of events (%)	**30 (34.9)**	**51 (60)**
Objective Progression	27 (31.4)	48 (56.5)
Death without Objective Progression	3 (3.5)	3 (3.5)
Censored (%)	**56 (65.1)**	**34 (40.0)**
Study Termination	38 (44.2)	17 (20.0)
Adverse Event	12 (13.9)	4 (4.7)
Patient refused further treatment/ Investigator discretion	3 (3.5)	2 (2.3)
Removed due to global deterioration of health status	0 (0.0)	4 (4.7)
Protocol violation	2 (2.3)	2 (2.3)
No on-study tumor assessment (due to cycle 1 death)	0 (0.0)	2 (2.3)
Inadequate baseline or ≥ 2 consecutive missing assessments	0 (0.0)	2 (2.3)
Missed ≥ 4 weeks of treatment or lost to follow-up	1 (1.2)	1 (1.2)
Median (months)	11.4	5.5
95% CI	(7.4, 19.8)	(3.6, 7.4)
Adjusted Hazard Ratio	0.418	
95% CI	(0.263 to 0.662)	
p- value*	0.000118*	

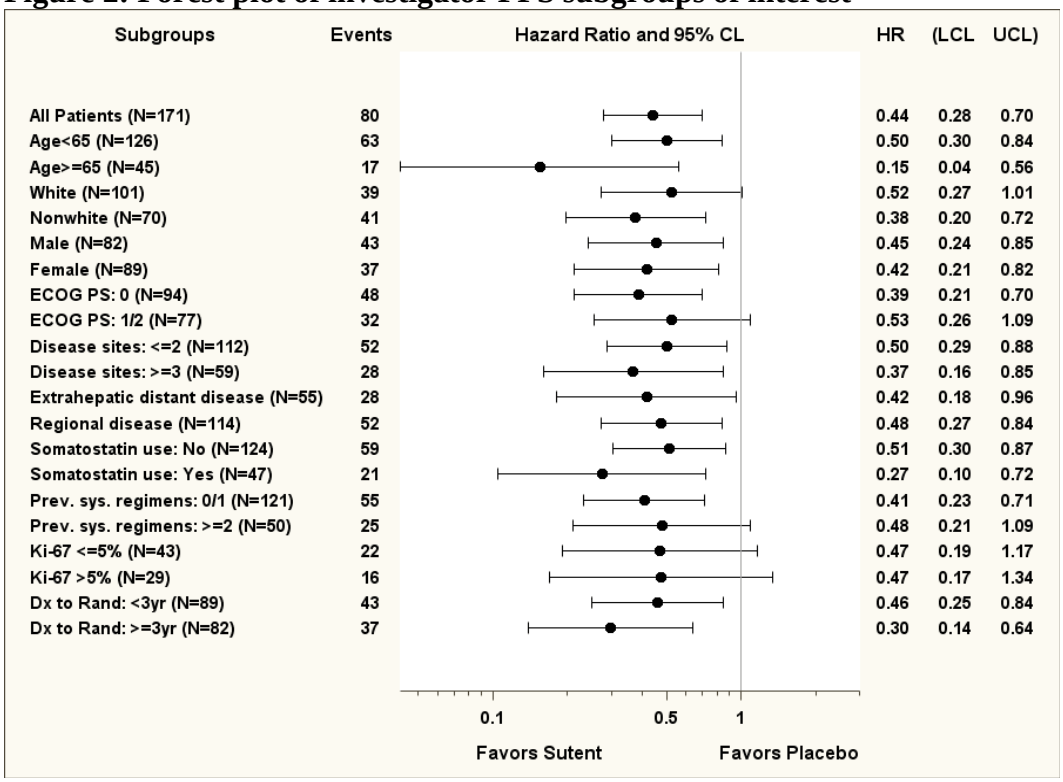
*p-values are unadjusted for multiple data looks and early study termination.

Figure 1: KM curve of investigator PFS - ITT Population



Subgroup analyses of PFS tended to favor the sunitinib arm, as depicted in figure 2.

Figure 2: Forest plot of investigator PFS subgroups of interest



HR = hazard ratio (Sunitinib vs. Placebo); LCL = lower confidence limit of HR; UCL = upper confidence limit of HR

6.3.2.2 *Post-hoc* Blinded Independent Central Radiologic Review (BICR)

As requested by the FDA, the sponsor retrospectively performed a blinded independent central radiologic review (BICR) of scans from study A6181111. The BICR was performed in accordance with a radiology review charter according to a two-reader, two-time point lock, followed by a sequential locked read, batch mode paradigm with the reading radiologists blinded to treatment arm, outside radiology reports, investigator assessments, and adverse events. Discrepancies in dates of disease progression between these radiologists were adjudicated by a third radiologist who determined which interpretation (Reader 1, Reader 2, or a third interpretation) was to be used in the analysis.

The collection of scans began in September 2009. Of the 171 subjects on study A6181111, scans were received from 170 subjects (99.4%) and complete image sets/time points with acceptable image quality were collected for 160 subjects (93.6%). The BICR was unable to obtain complete scans on 7 subjects randomized to sunitinib and 4 subjects randomized to placebo.

Table 3 summarizes the BICR PFS analysis. This analysis reveals fewer events and higher rates of censoring. The overall concordance rate between the investigator and BICR for PFS was 57% (66% concordance on sunitinib arm, 48% concordance on the placebo arm). The overall concordance rate between the two central reviewers was 66% (70% concordance on sunitinib arm, 62% concordance on placebo arm).

Table 3: BICR PFS analysis

	Sunitinib (n=86)	**Placebo (n=85)**
Number of events (%)	22 (25.6)	39 (45.9)
Censored (%)	64 (74.4)	46 (54.1)
Median (months) 95% CI	12.6 (9.4, 20.6)	5.8 (3.7, 7.2)
Adjusted Hazard Ratio 95% CI p- value*	0.315 (0.181, 0.546) 0.000015*	

*p-values are unadjusted for multiple data looks.

6.3.2.3 FDA analysis of PFS

In the initial review cycle of the sunitinib PNET efficacy supplement, FDA analysis of the submitted data sets and case report forms found 20 subjects (11.7%) who had improper PFS data, mainly due to misapplication of RECIST criteria or mishandling of missing assessments.

In their resubmission, the sponsor recalculated PFS using a 'derived overall tumor assessment' (DOTA) by re-evaluating the investigator raw tumor measurements using proper RECIST and censoring for missing assessments. In the sponsor's DOTA analysis, there was concordance with FDA's initial analysis in 17 of the 20 subjects, and discordance with the FDA's assessment in 3 of the 20 subjects (2 sunitinib, 1 placebo). The sponsor's DOTA found an additional 21 subjects (10 sunitinib, 11 placebo) whose PFS data differed from the investigator's assessment when deriving from the raw tumor measurements.

In the second review cycle, FDA conducted an analysis of the sponsor's DOTA. Of the 3 subjects where the sponsor differed with FDA's initial analysis, FDA agreed with the sponsor's new analysis in 1 case. Of the 21 new discrepant subjects found in DOTA, FDA disagreed with six, either disagreeing on whether an event occurred (based on $\geq$ 20% increase in sum of tumor measurements) or the date of the event. In addition, FDA re-analysis changed two patients (both placebo) from 'censor' to 'event' due to death during cycle 1. FDA re-analysis of PFS is summarized in Table 4.

Table 4: FDA re-analysis of PFS

	Sunitinib (n=86)	**Placebo (n=85)**
Number of events (%)	32 (37)	50 (59)
Censored (%)	54 (63)	35 (41)
Median (months) 95% CI	10.2 (7.4, 16.9)	5.4 (3.4, 6.0)
Adjusted Hazard Ratio 95% CI p-value*	0.427 (0.271 to 0.673) 0.000146*	

*p-values are unadjusted for multiple data looks and early study termination.

6.3.2.4 Summary of PFS analyses

In all PFS analyses, including sensitivity analyses performed by the FDA and sponsor, sunitinib improves progression-free survival in patients with well-differentiated PNET. However, there remains an uncertainty about the magnitude of the PFS effect with sunitinib (given early termination of the trial; see section 6.3.2.5), and the relevance of PFS in this disease setting. Table 5 summarizes the three main PFS analyses. Given that efficacy data was analyzed by the DMC at 20, 50, and 73 PFS events (section 6.3.1), those early data looks should be adjusted for; otherwise, the type I error will be inflated.

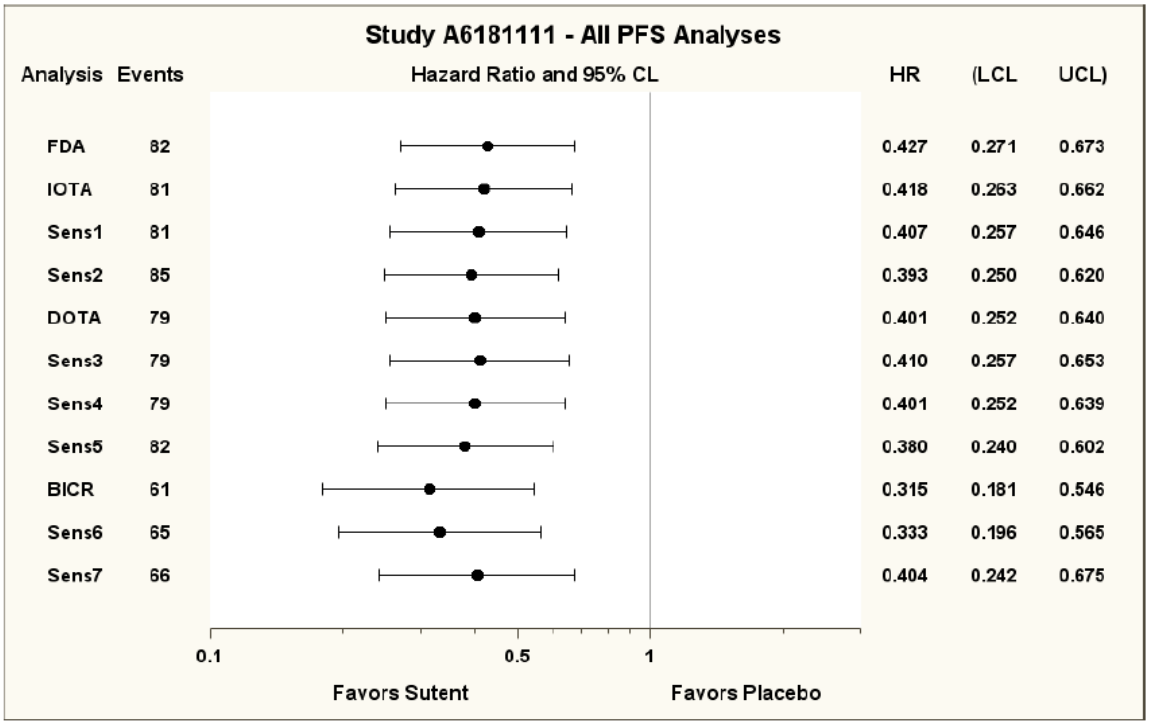
Table 5: Summary of PFS analyses

PFS analysis	**Number events**	**Number censored**	**Difference in median PFS**	**HR**	**Does p value cross adjusted efficacy boundary*?**
Investigator	81	90	5.9 months	0.42	No
Central Radiology	61	110	6.8 months	0.32	Not applicable
FDA	82	89	4.8 months	0.43	No

* When accounting for prior looks at the PFS data by the DMC

A Forest plot of several PFS analyses performed by the FDA and sponsor showed the hazard ratios (HRs) favored sunitinib in all the PFS analyses, and are generally consistent across analyses (Figure 3).

Figure 3: Forest plot of PFS analyses



HR = hazard ratio (Sunitinib vs. Placebo); LCL = lower confidence limit of HR; UCL = upper confidence limit of HR; IOTA = Investigator Overall Tumor Assessment; DOTA = Derived Overall Tumor Assessment; BICR = Blinded Independent Central Radiology

6.3.2.5 Potential Overestimation of Magnitude of PFS Treatment Effect

Interpretation of results based on early data looks is challenging, especially with a relatively subjective primary endpoint such as PFS. General issues with early PFS analyses include inadequate follow-up, missing assessments, high rates of censoring, and inability to provide an accurate and reproducible estimate of the treatment effect size.

It has been well-recognized that overestimation of the true treatment effect can occur in trials with multiple data looks that stop early for efficacy (Ellenberg SS *et al* JAMA 2010). In group sequential designs, when data are assessed repeatedly over time, a random high that overestimates the true effect is more likely with early analysis of the data. Thus, the PFS results from Study A6181111, which was stopped early based on the observation of less than 30% of the planned number of events, likely overestimated the true treatment effect size.

6.3.3 Analysis of Secondary Endpoints

6.3.3.1 Overall Survival

According to the A6181111 protocol, OS was to be updated every 2 years until 95% of enrolled subjects have died, or at 5-year follow-up. The study was not powered for OS and OS analysis was not event-driven.

The first OS analysis was performed at study termination (April 2009) at the time of PFS analysis, when there was no cross-over from placebo to sunitinib. The death rate at the April 2009 analysis was only 18%. In the two subsequent analyses in December 2009 and June 2010, there was 69% cross-over to sunitinib, and event rates of 30% and 43%, respectively. The low event rates and the high cross-over make the OS data difficult to interpret.

At study termination, April 15, 2009, with a median follow-up of 10.2 months for the sunitinib arm and 11.1 months for the placebo arm, there were 30 deaths reported among the 171 patients, 9 deaths on the sunitinib arm versus 21 deaths on placebo. The corresponding HR was 0.409 (95% CI 0.187, 0.894). At the December 2009 cut-off, OS analysis revealed a HR of 0.594 (95% CI 0.340, 1.038). The most recent OS update, using a June 1, 2010 cut-off, showed a HR of 0.737 (95% CI 0.465, 1.168) as depicted in Table 6.

Table 6: Overall survival update as of June 2010

	Sunitinib (n=86)	**Placebo (n=85)**
Number of deaths (%) Subjects who Died on Study Subjects who Died during follow-up	34 (39.5) 5 29	39 (45.9) 9 30
Number Censored (%)	52 (60.5)	46 (54.1)
Hazard Ratio (95% CI)	0.737 (0.465 to 1.168)	

6.3.3.2 Objective Response Rate

The sponsor reported eight sunitinib treated subjects with an objective response, with six partial responses (PR) and two complete responses (CR). The sponsor's objective response rate (ORR) for sunitinib was 9.3%, and 0% for placebo. An FDA analysis revealed that two of the eight patients who the sponsor classified as a responder did not have a subsequent scan confirming the response. In addition, the FDA re-classified the two CRs to PR given that there was measurable tumor documented at best response. According to FDA analysis, the ORR for sunitinib was 7%, and all six were PRs. The median duration of response for these six patients was 42.8 weeks, although five of these subjects had an ongoing response at study termination.

6.3.3.3 Patient-reported outcomes (PRO)

Patients completed the 15-domain EORTC QLQ-C30 questionnaire at baseline, every 4 weeks, and at the end of treatment/ withdrawal. This PRO consists of 3 independent domains: global health-related quality of life (HRQoL), functional scales (cognitive, emotional, physical, role and social functioning), and symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, and pain).

The sponsor's statistical analysis used the minimal important difference (MID) approach. In the MID approach, clinical significance is defined as a $\geq$ 10 point mean change from baseline (on a 0-100 point scale). To adjust for potential impact of differences in baseline scores on treatment effect, the baseline scores were included in a repeated measures mixed effects model as a covariate for all 15 subscales.

Baseline and at least one post-baseline QLQ-C30 score was available for only 73 sunitinib (85%) and 71 (84%) placebo subjects. The sponsor reported that subjects in the sunitinib arm had overall clinically and statistically significant worsening of diarrhea. The sponsor reported no differences between treatment arms in the other symptom scales. With respect to the Global HRQoL and the functional scales, the sponsor reported no clinically or statistically significant differences between treatment arms in mean change from baseline.

6.4 Safety Results

The Safety analysis of sunitinib on Study A6181111 revealed an adverse event profile consistent with the known safety profile of this drug in Renal Cell Carcinoma and Gastrointestinal Stromal Tumor. Common adverse events include: diarrhea, nausea/ vomiting, fatigue/ asthenia, hypertension, hand-foot syndrome, stomatitis, neutropenia, and thrombocytopenia. Rare but serious adverse events on the sunitinib arm included leukoencephalopathy, intracranial hemorrhage, renal failure, hepatic toxicity, ventricular arrhythmia, and cardiac failure. There were 2 patients on sunitinib who died of cardiac failure. Of these 2 cardiac failure deaths, one patient died on-study with concomitant

renal failure and hepatic failure, and the other died approximately 2 months after study withdrawal.

6.4.1 Exposure Summary

The target dose of sunitinib was 37.5 mg continuous daily dosing. Subjects not experiencing response and experiencing grade 1 or less non-hematological or grade 2 or less hematological toxicity within the first 8 weeks were permitted to escalate to 50 mg daily at any time after 8 weeks. Dose reduction was permitted for treatment-related toxicity. Data for exposure is summarized in Table 7.

Table 7: Summary of Dose Administration

	Sunitinib N=83	**Placebo N=82**
Median Duration of Exposure (days)	141 (13 - 602)	113 (1 - 614)
Dose Interruptions	25 (30.1%)	10 (12.2%)
1 Dose Reduction	24 (28.9%)	9 (11.0%)
$\geq$ 2 Dose Reductions	2 (2.4%)	0
Dose Escalation	8 (9.6%)	20 (24.4%)

6.4.2 Deaths

As of the study termination date on April 15, 2009, 9 patients who were randomized to sunitinib died (5 on study, 4 during follow-up) and 21 patients who were randomized to placebo died (9 on study deaths, 12 deaths during follow-up). On-study deaths were defined as those deaths that occurred after the first dose of study drug and within 28 days of the last dose of study medication.

Of the 9 patients who died on the sunitinib arm as of the April 15, 2009 cut-off, two died of cardiac failure and the other seven died of disease progression.

6.4.3 Nonfatal Serious Adverse Events (SAE) and Grade 3-4 Adverse Events

Treatment emergent SAEs were reported in 22 of 83 (26.5%) of sunitinib-treated patients and 34 of 82 (41.5%) placebo-treated patients.

SAEs of special interest on the sunitinib arm include intracranial hemorrhage, acute renal failure, and leukoencephalopathy. All of these are listed in the product label.

Table 8 summarizes the most common grade 3-4 adverse events.

Table 8: Grade 3-4 Adverse Events in > 2% of patients on either treatment arm

	Sunitinib N=83	**Placebo N=82**
Neutropenia	12%	0%
Hypertension	9.6%	1.2%
Palmar-plantar erythrodysesthesia syndrome	6%	0%
Leukopenia	6%	0%
Diarrhea	4.8%	2.4%
Asthenia	4.8%	3.7%
Fatigue	4.8%	8.5%
Abdominal Pain	4.8%	9.8%
Hypoglycemia	4.8%	1.2%
Stomatitis	3.6%	0%
Thrombocytopenia	3.6%	0%
Anorexia	2.4%	1.2%
Vomiting	0%	2.4%
Back Pain	0%	4.9%
Musculoskeletal Pain	0%	2.4%

6.4.4 Common Adverse Events

The most common adverse events are consistent with the known toxicity profile of sunitinib and included diarrhea, nausea/vomiting, asthenia/fatigue, hair color changes, neutropenia, hypertension, palmar-plantar erythrodysesthesia syndrome, stomatitis/ mucosal inflammation, dysgeusia, epistaxis, rash, and thrombocytopenia. Table 9 outlines the most common AEs observed in the sunitinib and placebo arms.

Table 9- Grade 1-4 Adverse Events in > 15% of patients on either treatment arm

	Sunitinib N=83	**Placebo N=82**
Diarrhea	59.0%	39.0%
Nausea	44.6%	29.3%
Asthenia	33.7%	26.8%
Vomiting	33.7%	30.5%
Fatigue	32.5%	26.8%
Hair color changes	28.9%	1.2%
Neutropenia	28.9%	3.7%
Abdominal pain	27.7%	31.7%
Hypertension	26.5%	4.9%
Palmar-plantar erythrodysesthesia syndrome	22.9%	2.4%
Anorexia	21.7%	20.7%
Stomatitis	21.7%	2.4%
Dysgeusia	20.5%	4.9%
Epistaxis	20.5%	4.9%
Headache	18.1%	13.4%
Insomnia	18.1%	12.2%
Rash	18.1%	4.9%
Thrombocytopenia	16.9%	4.9%
Mucosal inflammation	15.7%	7.3%
Weight decreased	15.7%	11.0%
Constipation	14.5%	19.5%
Back pain	12.0%	17.1%

6.4.5 Discontinuations due to Adverse Event

There were 12 sunitinib patients and 10 placebo patients who were discontinued and censored in the sponsor's PFS analysis for either adverse events, global deterioration of health status, or cycle 1 death with no on-study tumor assessment. Table 10 summarizes these discontinuations.

Table 10: Discontinuations for adverse events, global deterioration, or cycle 1 death

	Sunitinib N=83	**Placebo N=82**
Fatigue/ Asthenia	4 (4.8%)	0
Diarrhea[1]	2 (2.4%)	0
Cardiomyopathy[2]/ Cardiac Failure	2 (2.4%)	0
Spinal Compression Fracture	1 (1.2%)	0
Mucosal Inflammation	1 (1.2%)	0
Neutropenia	1(1.2%)	0
Leukoencephalopathy	1 (1.2%)	0
General Deterioration Health Status	0	4 (4.9%)
Death in cycle 1 (no on-study assessment)	0	2 (2.5%)
Pleural effusion	0	1 (1.3%)
Cerebrovascular accident	0	1 (1.3%)
Abdominal pain	0	1 (1.3%)
Nausea/vomiting	0	1 (1.3%)

[1]One of these patients taken off for diarrhea also had biliary obstruction of minor papillae with biopsy-proven infiltrative PNET on ERCP.
[2]One patient taken off for grade 2 cardiomyopathy also had hypertension.

7 Conclusions

The multicenter, international, double-blind, randomized, placebo-controlled study A6181111 in patients with progressive, locally-advanced or metastatic well-differentiated pancreatic neuroendocrine tumors demonstrated an approximate 5 to 6 month improvement in median PFS for sunitinib and a reduction in the relative risk of PFS by > 50%. The PFS analysis was relatively consistent between investigator analysis, FDA analysis, and central radiologic review. However, the effect size is likely an overestimate due to multiple looks at the data and early termination of the study.

Analysis of OS was complicated by a low event rate and high cross-over rate from placebo to sunitinib, rendering interpretation of OS results problematic. Patient-reported outcome analysis showed no significant differences between the placebo and sunitinib treatment arms, except for a worsening of diarrhea symptom scale with sunitinib. Safety was generally consistent with the known toxicity profile of sunitinib, with two deaths on the sunitinib arm related to cardiac failure.

Items for ODAC discussion include the early termination of the trial, which likely overestimated the magnitude of PFS effect, and the benefit:risk of sunitinib in well-differentiated PNET, which is rare, can be relatively indolent, and for which there are few available therapies.