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Sponsor: Pfizer, Inc.

Investigational Product: Sunitinib malate (SU011248, SUTENT®)

Clinical Study Report Synopsis: Protocol A6181202

Protocol Title: A single-arm open-label international multi-center study of the efficacy and safety of sunitinib malate (SU011248, SUTENT®) in patients with progressive advanced metastatic well-differentiated unresectable pancreatic neuroendocrine tumors

Investigators: [redacted] (* did not randomize patients)

Study Centers: Australia (2 sites), Belgium (1 site), China (9 sites), Czech Republic (2 sites), Estonia (1 site), France (3 sites), Hungary (1 site), India (1 site), Italy (2 sites), Japan (2 sites), Norway (1 site), Netherland (1 site), Poland (2 sites), Portugal (1 site), Romania (2 sites), Slovakia (1 site), South Africa (1 site), Spain (2 sites), United States (4 sites)

Publications Based on the Study: None

Study Initiation and Completion Dates: First Patient First Visit: 06 June 2012 to ongoing at data cutoff 19 March 2016

Report Date: 11 November 2016

Previous Report Dates: 07 October 2016

Phase of Development: Phase 4

Study Objectives:

Primary Objective

To confirm sunitinib treatment effect on progression-free survival (PFS) per investigator assessment in patients with advanced/metastatic, well-differentiated, unresectable pancreatic neuroendocrine tumors (pNETs) per Response Evaluation Criteria in Solid Tumors (RECIST 1.0).

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Secondary Objectives

- To assess PFS per independent radiological review;
- To assess time to tumor progression (TTP);
- To assess overall survival (OS);
- To assess objective response rate (ORR);
- To assess duration of response (DoR);
- To assess time to tumor response (TTR);
- To evaluate the use of Choi criteria;
- To evaluate Chromogranin A (CgA) response;
- To assess the safety and tolerability of sunitinib;
- To assess patient-reported outcomes (PROs);
- To explore the potential relationship between plasma soluble kinase insert domain for tyrosine (sKIT) levels and measures of efficacy including PFS;
- To assess sunitinib and SU12662 (active metabolite of sunitinib) plasma trough concentrations (C_{trough}) and to potentially explore the relationship between C_{trough} and safety, biomarker, and efficacy.

METHODS

Study Design: This study was a multinational, multi-center, open-label, Phase 4 clinical trial evaluating the efficacy and safety of sunitinib in patients with progressive, advanced/metastatic well-differentiated, unresectable pNETs.

A minimum target enrollment of approximately 80 men and women 18 years of age or older with progressive advanced/metastatic well-differentiated unresectable pNETs was established for this study population. Of these 80 patients, approximately 40 patients were not to have received any previous systemic therapies (ie, first-line systemic treatment-naïve cohort), including chemotherapy, immunotherapy, intravenous peptide receptor radiotherapy, or investigational anticancer agent other than somatostatin analogs. The remaining approximately 40 patients were to have experienced progressive disease on or after prior systemic therapy (ie, later-line/previously treated).

Patients had to have experienced documented disease progression within a year prior to the start of study enrollment. Eligible patients were enrolled to receive sunitinib orally at

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37.5 mg once a day on a continuous daily dosing (CDD) schedule. After discontinuation of treatment and mandated 28-day follow-up, patients were followed to collect information on further antineoplastic therapy and survival.

Diagnosis and Main Criteria for Inclusion: Patients were to be 18 years of age or older; have proven diagnosis of well-differentiated pNET with available Ki-67 index, and unresectable or metastatic disease documented on a scan and disease progression within 12 months prior to study enrollment. Presence of at least one measurable target lesion according to RECIST 1.0; adequate organ function; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Study Treatment:

Eligible subjects were enrolled to receive sunitinib orally at 37.5 mg once a day on a CDD regimen. Study medication, sunitinib, was supplied as hard gelatin oral capsules containing 12.5 mg and 25 mg equivalents of sunitinib free base. Cycles were defined as a 28-day period.

Efficacy Evaluations:

Primary Efficacy Endpoint:

PFS per investigator assessment according to RECIST 1.0: time from date of enrollment to first progression of disease or death for any reason in the absence of documented progressive disease (PD), whichever occurred first. If tumor progression data included more than 1 date, the first date was used. PFS (in months) was calculated as (first event date − enrollment date +1)/30.4.

Secondary Efficacy Endpoints:

PFS per independent radiological review according to RECIST 1.0: time from enrollment to first documentation of objective tumor progression or to death due to any cause, whichever occurred first.

TTP: time from enrollment to first documentation of objective tumor progression. If tumor progression data included more than 1 date, the first date was used. TTP (in months) was calculated as (first event date − enrollment date +1)/30.4.

TTR: time from date of enrollment to first documentation of objective tumor response that was subsequently confirmed. For patients proceeding from partial response (PR) to complete response (CR), the onset of PR was taken as the onset of response. If lesion assessment data included more than 1 date, the first date was used. TTR (in months) was calculated as (first response date – enrollment date + 1)/30.4. TTR was only calculated for the subgroup of patients with an objective tumor response.

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OS: time from date of enrollment to date of death due to any cause. OS (in months) was calculated as (date of death − enrollment date +1)/30.4. For patients still alive at the time of the analysis or without confirmation of death, the OS time was censored on the last date they were known to be alive. Patients lacking data beyond enrollment had their OS times censored at enrollment with a duration of 1 day.

DoR: time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. DoR was calculated as (the end date for DoR − first CR or PR that was subsequently confirmed +1)/30.4. DoR (in months) was only calculated for the subgroup of patients with a confirmed objective tumor response. For patients proceeding from PR to CR, the onset of PR was taken as the onset of response.

ORR: percent of patients with confirmed CR or confirmed PR according to the RECIST 1.0, relative to all enrolled patients. Confirmed responses were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. Designation of best response of stable disease (SD) required the criteria to be met at least 6 weeks after enrollment. Patients who did not have on-study radiographic tumor re-evaluation, who received antitumor treatment other than the study medication prior to reaching a CR or PR, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR.

CgA response rate: percent of patients with a confirmed CgA CR or confirmed CgA PR, relative to the population with an elevated baseline CgA value. CR was defined as a decrease from a high baseline value to one that fell within the normal range, and a PR was defined as a decrease from a high baseline value to one that was at least 50% lower, but remained greater than the ULN range for CgA. PD was defined as at least a 50% increase in CgA level. Confirmed responses were those that persisted at least 4 weeks after initial documentation of response. Designation of best response of SD required the documentation of SD (<50% increase and <50% decrease from baseline) for at least 6 weeks.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

Plasma samples for determination of sKIT concentrations were obtained pre-dose on Days 1 and 15 of Cycle 1, Cycle 2 Day 1, Cycle 3 Day 1, and then every 2 cycles thereafter (Cycles 5, 7, 9, etc), and at the End of Treatment or time of investigator-assessed disease progression whenever possible.

Analysis of plasma samples was conducted at Intertek Pharmaceutical Services (Alta Bioscience Ltd). The sKIT was analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA) kit.

In cases where readings were below the level of quantification (BLQ) for the assay, such readings have been excluded from the analyses.

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Ki-67 tumor index was collected at Screening as part of medical history. Ki-67 assessments based on previous tumor biopsy results or previous surgical resections had to be provided.

Plasma samples for determination of the trough concentrations (pre-dose) levels of sunitinib and SU012662 were obtained pre-dose at Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 5. For each PK sample, actual time and date of sample collection in addition to the actual time and date of the last dose before sample collection were appropriately recorded on the case report form. Samples were analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

A 4 mL blood sample Prep D1 (dipotassium ethylenediamine tetraacetic acid whole blood collection optimized for deoxyribonucleic acid analysis) was collected at the baseline visit and retained for potential pharmacogenomic analyses related to drug response. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The retained pharmacogenomic samples were collected from all patients unless prohibited by local regulations.

Patient-reported outcomes (PROs) defined as health-related quality of life (QoL) using the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ Gastrointestinal (GI) NET-21 (EORTC QLQ-G.I.NET21). The questionnaire was to be self-administered by the patient in the clinic. The questionnaire was to be completed before any interventions (eg, laboratory assessments or study drug administration) at baseline, every cycle post-baseline assessment including at the End of Treatment or withdrawal, and the visit 28 days post-treatment. In the event the patient was unable to visit the clinic for the 28 days post-treatment visit, assessments were not applicable.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure, temperature, weight), 12-lead electrocardiograms (ECGs), adverse events (AEs), safety laboratory tests, ECOG performance status, physical examination.

Statistical Methods: Detailed methodology for summarization and statistical analyses of the data collected in this trial was documented in a Statistical Analysis Plan (SAP).

RESULTS

Patient Disposition and Demography: A total of 123 patients were screened for this study (A6181202), of whom 106 received sunitinib treatment (61 patients in the treatment-naïve cohort and 45 patients in the later-line cohort). Sixty-eight (68) patients were still ongoing (either on treatment or in long-term survival follow-up) at the time of data cutoff (Table S1).

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Table S1. Patient Disposition

Screened = 123	Treatment-Naïve Cohort		Later-Line Cohort		Total	
	N	(%)	N	(%)	N	(%)
Assigned to Study	61		45		106	
Treated	61	(100.0)	45	(100.0)	106	(100.0)
Discontinued from Study	16	(26.2)	22	(48.9)	38	(35.8)
Patient Died	10	(16.4)	19	(42.2)	29	(27.4)
Relation to Study Drug not Defined	6	(9.8)	3	(6.7)	9	(8.5)
Lost to Follow-up	4	(6.6)	1	(2.2)	5	(4.7)
Other	0		2	(4.4)	2	(1.9)
Patient Refused Further Follow-up	2	(3.3)	0		2	(1.9)
Ongoing at Date of Cutoff	45	(73.8)	23	(51.1)	68	(64.2)
Discontinuations from Treatment	43	(70.5)	39	(86.7)	82	(77.4)
Patient Died	1	(1.6)	1	(2.2)	2	(1.9)
Relation to Study Drug not Defined	36	(59.0)	30	(66.7)	66	(62.3)
Global Deterioration of Health Status	2	(3.3)	2	(4.4)	4	(3.8)
Objective Progression or Relapse	26	(42.6)	23	(51.1)	49	(46.2)
Other	4	(6.6)	4	(8.9)	8	(7.5)
Patient Refused Continued Treatment for Reason Other Than Adverse Event	4	(6.6)	1	(2.2)	5	(4.7)
Related to Study Drug	4	(6.6)	5	(11.1)	9	(8.5)
Adverse Event	4	(6.6)	5	(11.1)	9	(8.5)
Not Related to Study Drug	2	(3.3)	3	(6.7)	5	(4.7)
Adverse Event	2	(3.3)	3	(6.7)	5	(4.7)

Full Analysis Set = all patients who were enrolled into the study regardless of whether patients received study drug or not.
Safety Analysis Set = all patients who received at least 1 dose of study medication.
Note: Percentage is based on the enrolled number of patients in each cohort.

All 106 patients enrolled into the study comprised the full analysis set (FAS) and were analyzed for efficacy, 61 patients in the treatment-naïve cohort and 45 patients in the later-line cohort. All patients in the FAS received at least a dose of sunitinib and were also included in the safety analysis set.

Data from the 61 treatment-naïve patients in the FAS were combined with the data from the treatment-naïve patients in the intention-to-treat population in A6181111 for the primary PFS analysis and pre-defined secondary efficacy analyses (ORR and OS). There were 76 first-line patients (41 treated with sunitinib and 35 treated with placebo) in Study A6181111. Thus, in the combined data there were 102 treatment-naïve patients that received sunitinib and 35 patients that received placebo.

The overall FAS population of this study was comprised of 63 (59.4%) male and 43 (40.6%) female patients. The mean age, mean weight, and mean height of the FAS were 54.6 years, 70.3 kg, and 169.1 cm, respectively. The majority of the demographic and baseline

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characteristics were similar between the 2 cohorts; however, the proportion of female and Asian patients was smaller in the later-line cohort.

All patients had an ECOG PS of 0 (64.2%) or 1 (35.8%) at baseline without notable differences between the 2 cohorts.

All patients had measurable disease at baseline and adequate baseline assessment. Overall, the majority of patients had lesions in the liver (98 [92.5%] patients) and pancreas (47 [44.3%] patients). Patients most commonly had 1, 2 or 3 involved disease sites. The treatment-naïve cohort had a larger proportion of patients with 1 involved disease site, compared to the later-line cohort (39.3% and 20.0%, respectively). A smaller proportion of patients in the treatment-naïve cohort had lesions in the pancreas (36.1%) than in the later-line cohort (55.6%).

Prior somatostatin analog therapy (SSA) was reported for 51 (48.1%) patients with 24 (39.3%) patients in the treatment-naïve cohort and 27 (60.0%) patients in the later line cohort. Patients with regimens that consisted only of SSAs were considered naïve.

In regards to loco regional treatment at screening, the most common were trans arterial chemoembolization (treatment-naïve cohort: 23.0%; later line cohort: 13.3%) followed by radiofrequency ablation (treatment-naïve cohort: 1.6%); later-line cohort: 6.7%). Patients who received previous chemoembolization without exposure to prior systemic chemotherapy were considered treatment-naïve.

In general, the demographic characteristics from Study A6181111 were comparable to the treatment-naïve cohort in this study (A6181202).

Efficacy Results:

Study A6181202 Alone

The primary analysis showed that the median PFS as assessed by investigator was 13.2 months (95% CI: 10.9, 16.7). The median PFS as assessed by investigator was 13.2 months (95% CI: 7.4, 16.8) and 13.0 months (95% CI: 9.2, 20.4) in the treatment-naïve cohort and the later-line cohort, respectively (Table S2). A median PFS of 11.1 months (95% CI: 7.4, 16.6) was observed in the FAS based on the independent third-party radiology assessment according to RECIST 1.0 with a median PFS of 11.1 months (95% CI: 5.5, 16.7) in the treatment-naïve cohort and 9.5 months (95% CI: 7.4, 18.4) in the later-line cohort. The third-party assessments supported the primary investigator-assessed PFS analysis.

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Table S2 Progression-Free Survival (Based on the Investigator Assessment According to RECIST) Treatment-Naive Cohort vs. Later-Line Cohort - Full Analysis Set

	Treatment-Naive Cohort (N=61)	Later-Line Cohort (N=45)	Total (N=106)
Number with event	37 (60.7)	28 (62.2)	65 (61.3)
Type of event			
Progression of disease (PD)	35 (57.4)	26 (57.8)	61 (57.5)
Death without progression of disease	2 (3.3)	2 (4.4)	4 (3.8)
Number censored	24 (39.3)	17 (37.8)	41 (38.7)
Reason for censorship			
No adequate baseline assessments	0	0	0
No on-study disease assessments	0	0	0
Given new anti-cancer treatment prior to tumor progression	2 (3.3)	6 (13.3)	8 (7.5)
Unacceptable gap of >16 weeks between PD or Death to the most recent prior adequate assessment	0	3 (6.7)	3 (2.8)
In follow-up for progression	18 (29.5)	6 (13.3)	24 (22.6)
Removed from Study prior Documentation of PD or Death	4 (6.6)	2 (4.4)	6 (5.7)
Probability of being event free at Month 6[a] (95% CI[b])	66.7 [52.9, 77.4]	75.9 [58.7, 86.7]	70.5[60.2, 78.7]
Kaplan-Meier estimates of Progression Free Survival (Month) Quartiles (95% CI)[c]			
25%	5.0 [2.7, 7.4]	7.4 [3.7, 10.2]	5.6 [3.7, 7.5]
50%	13.2 [7.4, 16.8]	13.0 [9.2, 20.4]	13.2 [10.9, 16.7]
75%	20.2 [16.7, 26.2]	22.9 [14.7, 37.9]	22.9 [16.8, 33.2]

Abbreviations: CI = Confidence Interval; PD = Progression of Disease; PFS = Progression-Free Survival; RECIST= Response Evaluation Criteria In Solid Tumors

[a] Estimated from the Kaplan-Meier curve.

[b] Calculated from the product-limit method.

[c] Calculated from Brookmeyer and Crowley Method.

PFS is defined as the time from date of enrollment to first progression of disease (PD) or death for any reason in the absence of documented PD, whichever occurs first.

Comparisons were made regarding the independent third-party radiology assessment according to Choi criteria in addition to RECIST; the evaluation of tumor response according to Choi criteria has been considered particularly useful in patients with GIST to also capture changes in tumor density after treatment. A longer median PFS was observed in both cohorts compared to RECIST, with a median PFS of 18.7 months (95% CI: 5.6, not estimable) in the treatment-naïve cohort, and a median PFS of 16.5 months (95% CI: 7.4, 22.9) in the later-line cohort.

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Analyses of secondary efficacy endpoints supported the primary PFS analysis. The median TTP based on investigator assessment was 14.5 months (95% CI: 11.0, 16.7) in the FAS, with a median TTP of 14.8 months (95% CI: 7.5, 16.8) and 14.5 months (95% CI: 9.2, 20.4) for the treatment-naïve cohort and later line cohort, respectively. RECIST 1.0 confirmed ORR in the FAS based on investigator assessment was 24.5% (95% exact CI: 16.7, 33.8) with a CR rate of 2.8% and a PR rate of 21.7%. The ORR was 21.3% (95% exact CI: 11.9, 33.7) in the treatment-naïve cohort and 28.9% (95% exact CI: 16.4, 44.3) in the later line cohort. Responses were rapid, with a median TTR based on investigator assessment was 3.8 months (range: 1.0-11.1 months); there was no difference in median TTR between the treatment-naïve cohort and the later line cohort (both medians 3.8 months). Responses were also durable, with a median DoR based on investigator assessment of 14.7 months (95% CI: 10.1, 21.9); the median DoR in the treatment-naïve cohort was longer (19.1 months [95% CI: 10.1, not estimable]) than the median DoR in the later-line cohort (14.7 months [95% CI: 5.5, 21.9]).

In addition to PFS analysis according to Choi criteria, TTP was also analysed according to Choi and the median was 18.7 months (95% CI: 5.6, not estimable) for the treatment-naïve cohort and 16.7 months (95% CI: 7.4, 30.9) for the later-line cohort; which was greater than the investigator-assessed TTP by RECIST 1.0.. Furthermore, the ORR based on the independent third-party radiology assessment according to Choi criteria was higher than the ORR assessments according to RECIST 1.0: 52.5% (95% exact CI: 39.3, 65.4) and 55.6% (95% exact CI: 40.0, 70.4) in the treatment-naïve and later-line cohort, respectively. Although there was a trend in evaluating higher treatment response when Choi criteria were compared to RECIST criteria; however, further analysis is warranted to determine the role Choi criteria may play in assessing response in patients with pNET.

As the majority of patients were in follow-up at the time of data cutoff, the OS data were not mature as of the data cutoff date. An updated analysis of OS will be performed when the median OS can be accurately calculated and presented in a supplemental CSR.

In patients with confirmed CgA response, a greater proportion of patients in the treatment-naïve cohort had a confirmed objective CR or PR (16.4% [95% exact CI: 9.6, 32.5]) compared to the later line cohort (11.1% [95% exact CI: 4.0, 25.6]). However, a definitive conclusion on CgA response could not be made, as the sample size was small.

Combined Studies A6181202 and A6181111 Data

To strengthen the confirmed sunitinib treatment effect on PFS demonstrated in Study A6181202, PFS data from treatment-naïve patients in this study and Study A6181111 were combined and compared to PFS data from the placebo control arm of Study A6181111. A statistically significant and clinically meaningful improvement in investigator-assessed PFS was observed in favor of patients receiving sunitinib (ie, sunitinib arm treatment-naïve cohort) compared to patients receiving placebo (ie, placebo arm treatment-naïve cohort). A median PFS of 12.9 months (95% CI: 7.4, 16.7) was observed in the sunitinib arm treatment-naïve cohort, and a median PFS of 5.7 months (95% CI: 3.6, 7.9) was observed in

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the placebo arm treatment-naïve cohort, with an HR of 0.429 (95% CI: 0.245, 0.752) and a 1-sided p-value of 0.001 based on 50 events in the sunitinib arm treatment-naïve cohort and 19 events in the placebo arm treatment-naïve cohort. In order to ensure that the PFS endpoint was robust, an independent third-party radiology assessment according to RECIST 1.0 was conducted. A median PFS of 12.6 months (95% CI: 7.7, 16.6) was observed for the sunitinib arm treatment-naïve cohort and a median of 6.2 months (95% CI: 3.6, 8.1) for the placebo arm treatment-naïve cohort, with an HR of 0.552 (95% CI: 0.292, 1.042) and a 1-sided p-value of 0.031 based on 55 events (sunitinib arm treatment-naïve cohort: 41 [40.2%], placebo arm treatment-naïve cohort: 14 [40.0%]), which supported the robustness of the results of the primary investigator-assessed PFS analysis.

Controlling for baseline characteristics (age, ethnic origin, and performance status of PFS as assessed by Investigator) had no effect on the PFS HR as assessed by investigator (HR=0.424 [95% CI: 0.217, 0.827]) with a 1-sided p value of 0.005. The results of the sensitivity analysis supported the robustness of the primary analysis.

Patient-Reported Outcomes

The naïve cohort showed some declines in health-related QoL compared to the later-line cohort; however these changes manifest in later cycles. Conversely, the later-line cohort does not show notable declines in scales. In addition, both cohorts showed progressive decline in social functioning over time.

The combined cohort was not meaningful due to the scarcity of data from latter cycles from Study A6181111.

Pharmacokinetic and Pharmacodynamic Results:

Biomarkers

SKIT concentration was pharmacodynamically modulated upon sunitinib treatment. This observation is consistent with previous reports in patients with metastatic breast cancer and GIST. No statistically significant differences were seen when PFS curves were compared after stratification by median baseline sKIT concentration in the treatment-naïve and in the later-line cohorts. In the OS analysis in the treatment-naïve cohort, while OS data are still immature, the Kaplan-Meier estimate showed a potential trend in favor of patients with baseline sKIT ≥ median. However, this observation was not replicated in the later-line cohort but held in the combined cohorts.

No statistically significant differences were seen when PFS curves were compared after stratification by median baseline tumor Ki-67 index in the treatment-naïve and in the later-line cohorts. When OS curves were compared after stratification by median baseline tumor Ki-67 index in the treatment-naïve cohort, and while OS data are still immature, the Kaplan Meier estimation showed a trend in favor of the group with baseline tumor Ki-67 index ≥ median. However, this trend was not observed in the later-line cohort or in the

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combined cohorts. This observation is consistent with previous reports which showed sunitinib and/or everolimus may induce durable disease control in patients with well-differentiated pNET with a Ki-67 index above 15% and positive lesions on functional imaging with gallium^{68} dotatoc and/or Octreoscan®.

In summary, there were no clear predictive and/or prognostic biomarkers identified in this study for patients with advanced/metastatic, well-differentiated, unresectable pNETs with regard to PFS. With regard to OS, potential associations were observed in relation to baseline sKIT and Ki-67 index in the treatment-naïve cohort; however, the OS results are still immature and based on only few events. In addition, in the later-line cohort, the OS appeared to be similar between the sKIT or Ki-67 subgroups.

Pharmacokinetics and Pharmacokinetics-Pharmacodynamics

Another secondary objective of this study was to determine the C_{trough} values for sunitinib and its active metabolite SU012662 in pNET patients and to potentially explore the relationship between C_{trough} values and safety, efficacy, and biomarkers. Both sunitinib and its active metabolite appeared to reach steady state concentrations by Day 15 of Cycle 1. There appeared to be no additional accumulation of sunitinib and its active metabolite across subsequent cycles. Based on the results of the analyses exploring potential relationships between safety, efficacy, and biomarker parameters with Total Drug C_{trough} values on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3, there appeared to be weak correlations (ie, $r < 0.50$) between safety (ie, percent change from baseline in absolute neutrophil count, thrombocyte count, lymphocyte count, hemoglobin, and systolic blood pressure count) and biomarker (ie, fold change from baseline in sKIT) parameters with C_{trough} values. In addition, the incidence of any-grade palmar-plantar erythrodysesthesia syndrome, thrombocytopenia, hypertension, and anaemia appeared to be greater in patients with higher Total Drug C_{trough} values (ie, $\geq$ median C_{trough}) as compared to those with lower Total Drug C_{trough} values (ie, < median C_{trough}). Furthermore, the ORR (based on RECIST or CgA criteria) and median PFS appeared to be greater in patients with higher Total Drug C_{trough} values as compared to those with lower Total Drug C_{trough} values. There were no consistent trends with respect to median OS in patients with higher C_{trough} values as compared to those with lower C_{trough} values. Further analyses showed no correlations (ie, $-0.3<r<0.3$) between PFS or OS with C_{trough} values on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3.

Safety Results:

One hundred four (104) patients (98.1%) experienced at least 1 AE on sunitinib treatment, and 69 patients (65.1%) experienced Grade 3 or 4 AEs, which were generally manageable by dosing interruption (63.2%), dose reduction (18.9%), and/or supportive care. Neutropenia, diarrhoea, leukopenia, palmar-plantar erythrodysaesthesia syndrome, fatigue, and thrombocytopenia were the most commonly all-causality reported AEs. The most common treatment-related AEs in this study were consistent with those that have previously been reported with sunitinib, such as neutropenia, diarrhoea, leukopenia, thrombocytopenia, and palmar-plantar erythrodysaesthesia syndrome (Table S3). Twenty-six (26) patients (24.5%)

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experienced SAEs. Eighteen (18) patients (17%) discontinued treatment due to AEs, 10 of the 18 patients discontinued due to treatment-related AEs. There were no deaths due to treatment-related toxicity and all deaths were due to disease progression with the exception of 1 death in the later-line cohort with reason not clearly ascertainable. The sunitinib AE profile observed in this study was generally consistent with the known AE profile for sunitinib. There were no new safety findings identified in this study compared to those in Study A6181111 and previously reported sunitinib studies.

In summary, the sunitinib treatment effect was confirmed in patients with advanced/metastatic, well-differentiated, unresectable pNETs with an acceptable safety profile. The benefit/risk profile of sunitinib was confirmed to be favorable for this patient population.

Table S3. Summary of Key Treatment-Emergent Adverse Events Experienced by ≥15% of Patients in Any Cohort by Preferred Term, and Corresponding CTCAE Grade (Treatment-Related, All Cycles, All Grades and Grade 3/4)

	Treatment-Naïve Cohort (N=61)		Later-Line Cohort (N=45)		Total (N=106)	
Number (%) of Patients with Preferred Term Adverse Event	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Neutropenia	36 (59.0)	12 (19.7)	21 (46.7)	10 (22.2)	57 (53.8)	22 (20.8)
Diarrhoea	29 (47.5)	5 (8.2)	20 (44.4)	1 (2.2)	49 (46.2)	6 (5.7)
Leukopenia	25 (41.0)	4 (6.6)	21 (46.7)	3 (6.7)	46 (43.4)	7 (6.6)
Palmar-plantar erythrodysaesthesia syndrome	19 (31.1)	5 (8.2)	14 (31.1)	2 (4.4)	33 (31.1)	7 (6.6)
Thrombocytopenia	18 (29.5)	6 (9.8)	14 (31.1)	2 (4.4)	32 (30.2)	8 (7.5)
Fatigue	18 (29.5)	1 (1.6)	10 (22.2)	0 (0.0)	28 (26.4)	1 (0.9)
Dysgeusia	13 (21.3)	0 (0.0)	11 (24.4)	0 (0.0)	24 (22.6)	0 (0.0)
Nausea	9 (14.8)	0 (0.0)	13 (28.9)	1 (2.2)	22 (20.8)	1 (0.9)
Hypertension	14 (23.0)	4 (6.6)	7 (15.6)	2 (4.4)	21 (19.8)	6 (5.7)
Stomatitis	13 (21.3)	2 (3.3)	6 (13.3)	1 (2.2)	19 (17.9)	3 (2.8)
Dyspepsia	5 (8.2)	0 (0.0)	11 (24.4)	0 (0.0)	16 (15.1)	0 (0.0)

Abbreviations: AE=Adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities, N=Number of patients; PT=Preferred term; TEAE=Treatment Emergent Adverse Event.
Patients are counted once at the highest CTCAE grade on-study.
CTCAE v3.0 was used.
TEAEs are all AEs (serious and non-serious) occurred, for the first time, on or after the first day of study treatment. Events that are continuations of baseline abnormalities are considered TEAEs only if there is an increase in grade over baseline.
Maximum CTCAE Grade is defined as the maximum CTCAE grade value for the specific PT.
MedDRA (v19.0) coding dictionary applied.

2. CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

- The sunitinib treatment effect was confirmed in patients with advanced/metastatic, well-differentiated, unresectable pNET, with an investigator-assessed median PFS of 13.2 months (95% CI: 10.9, 16.7). The sunitinib treatment effect in for treatment-naïve pNET patients was strengthened by the combination of PFS data from the treatment-naïve cohort of Study A6181202 with PFS data from Study A6181111, where investigator-assessed median PFS of 12.9 months (95% CI: 7.4, 16.7) was observed for the sunitinib arm treatment-naïve cohort and 5.7 months (95% CI: 3.6, 7.9) was observed for the placebo arm treatment-naïve cohort with an HR of 0.429 (95% CI: 0.245, 0.752) and a p-value of 0.001.

- The independent third-party radiology assessment according to RECIST 1.0 supported the primary investigator assessed PFS analysis with a median PFS of 11.1 months (95% CI: 7.4, 16.6).

- The secondary endpoints (TTP and ORR) assessments according to RECIST supported the primary PFS endpoint with an investigator-assessed median TTP of 14.5 months (95% CI: 11.0, 16.7) and an investigator-assessed ORR of 24.5% (95% exact CI: 16.7, 33.8), with responses that were rapid and durable with an investigator-assessed median TTR of 3.8 months (range: 1.0-11.1 months) and an investigator-assessed median DoR of 14.7 months (95% CI: 10.1, 21.9).

- Although there was a trend in evaluating higher treatment response when Choi criteria were compared to RECIST criteria, further analysis is warranted to determine the role Choi criteria may play in assessing response in patients with pNET.

- A definitive conclusion on CgA response could not be made, as the sample size was small.

- Sunitinib was associated with AEs that were consistent with the known safety profile, generally manageable by dosing interruption, dose reduction, and/or supportive care.

- In terms of global health-related quality of life and functioning domains (EORTC QLQ-C30 and EORTC QLQ-G.I.NET21), the treatment-naïve cohort showed a decline earlier than the later-line cohort, however, these changes were seen in later cycles.

- Global health-related quality of life and functioning domains (EORTC QLQ-C30) were maintained for patients in the sunitinib arm treatment-naïve cohort with limited adverse symptomatic effects.

- sKIT concentrations were pharmacodynamically modulated, decreasing steadily while on sunitinib treatment until Cycle 7, at which time the concentrations reached a low plateau and did not change notably until the End of Treatment, at which point the concentrations still remained below the baseline concentrations but started rising again.

2. CLINICAL STUDY REPORT SYNOPSIS

- sKIT and Ki-67 were not identified as clear predictive and/or prognostic biomarkers in this study for patients with advanced/metastatic, well-differentiated, unresectable pNETs.

- Potential associations were observed in regard to OS in relation to baseline sKIT and Ki-67 index in treatment-naïve pNET patients; however, the OS results are still immature and based on only few events. In addition, in the later-line pNET patients, the OS appeared to be similar between the sKIT or Ki-67 subgroups.

- The steady state concentrations for sunitinib and its active metabolite were reached by Day 15 of Cycle 1 and did not show additional accumulation across subsequent cycles.

- The incidence of all grades AEs of palmar-plantar erythrodysaesthesia syndrome, thrombocytopenia, hypertension, and anaemia appeared to be greater in patients with higher Total Drug C_{trough} concentrations as compared to those with lower Total Drug C_{trough}.

- The ORR (based on RECIST or CgA criteria) and median PFS appeared to be greater in patients with higher Total Drug trough concentrations as compared to those with lower Total Drug trough concentrations.